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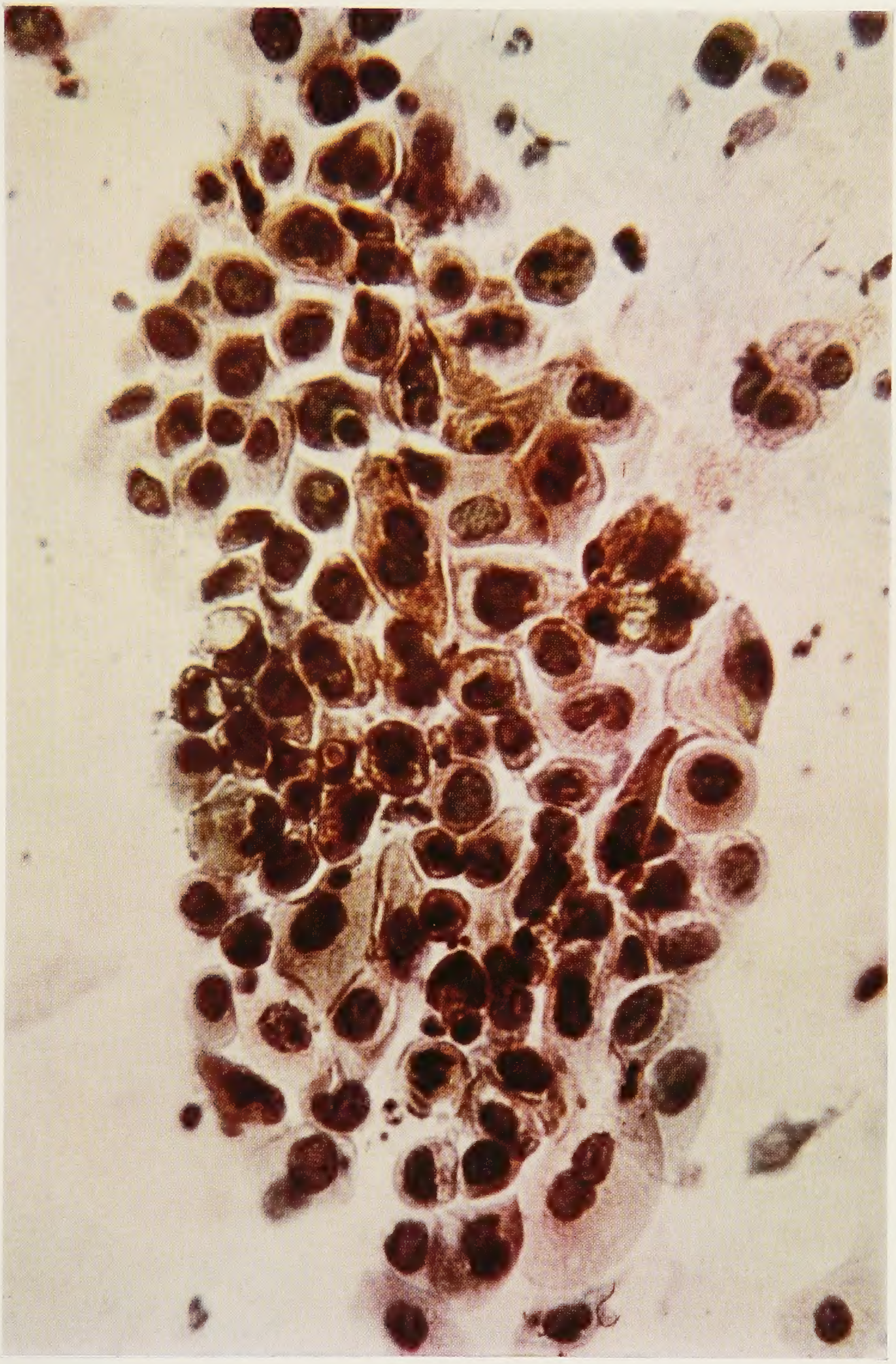

PLATE I

Carcinoma in-situ of the cervix. The cells tend to be round or oval in outline. Many of the nuclei make up more than fifty-per cent of the cells. The nuclei are hyperchromatic and clumpy. Several of the cells are multinucleated. The nuclear border tends to be irregular. The cells do not adhere to one another.

A TEXTBOOK OF GYNECOLOGY

By

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Printed in the United States of America

Dedicated to the memory of

DOCTOR THOMAS S. CULLEN
my Professor

A great contributor to Gynecology

Preface

The purpose of this book is to present in a brief and clear manner a new and modern summary of present-day gynecology.

Theories will be touched upon, but stress will be directed to the facts as known today. The object is to remove the chaff from the grain, to make perusal easy and rapid, and to invite the instructor to individualize his own methods of teaching. If textbooks covered every detail and philosophy, they would be too voluminous for practical purposes. This book may act as an outline for the teacher to elaborate and digress. In addition, it is intended to interest the practising physician who has never ceased being a student, and who may wish to follow the methods and approaches in this field today.

Everywhere in this book the basic pathology is stressed. Never has that part of this specialty been presented better than in Emil Novak's *Gynecologic and Obstetric Pathology*. Now the details presented are fewer, but they remain the basis on which gynecology is founded. After the pathology of the individual disease has been considered, the symptoms of the patient become more obvious and logically understood. Similarly, the diagnosis may be reached from the physical examination and laboratory findings more logically in the light of the understanding of the pathology. And finally, the treatment of the disease has its logical basis in combatting the pathological process. When it is difficult to understand the reason for a method of treatment, it is well that the mind of the physician be turned to the pathological findings. Frequently, as time passes, a diametrically opposite approach to treatment of a particular disease is accepted by the profession. There must be an explanation eventually available in every instance.

Certain operative techniques are described briefly, because even the general practitioner and internist may be interested in these methods. Gynecology has a strong Kellyian surgical background and includes almost half of all major surgery. The function, diagnosis and treatment of the numerous and variable gynecological malignancies make up a fascinating and complicated area of grave importance. The extra-ordinary effects of the hormones on the genital tissues, which includes even the skin of the entire body, are so striking as to cause obvious gross changes and numerous delicate variations in function.

In recent years, the effects of emotions and personality factors in women have been recognized to be of tremendous importance in genital function. The varying stimulation by the emotions of the autonomic nervous system, the vascular system in the pelvis, and finally the endocrine system, may be so profound as to cause major disability. These factors must be reckoned with daily in the understanding and treatment of gynecologic disease and studied constantly for greater understanding.

An uncommon feature of this book is its new types of illustrations. The author has foregone the use of the often-repeated cuts and offers completely new material. The new tone drawings are the work of one artist. The photomicrographs have been made by one medical photographer. It will be pleasing, perhaps, to view Kodachromes not previously published. These efforts are offered for the reader's interest.

At the end of each section in this book are listed a few choice references. Usually there are one or two historical references, one or two experimental papers, and finally, two or three modern clinical articles which may introduce the student to the literature in gynecology. The instructor may choose to make these references required reading, or may substitute others of his own choosing. The habits formed from an early approach to the literature may be extended throughout a medical career.

If this treatise aids physicians in their understanding of the large number of diseases of women, with the dramatic hormone relations, devastating cancers, and emotional upheavals, its purpose will have been realized.

L. A. G.

Acknowledgments

This volume would be incomplete if it did not recognize again, the masterful touch and artistry of a great gentleman, Mr. Charles C Thomas, and the executive ability and co-operative attitude of his son, Mr. Payne Thomas. The editorial genius of Mr. Warren H. Green has contributed greatly to the completion of this book. Doctor William K. Keller, Professor of Psychiatry at the University of Louisville, kindly consented to write the chapter on “Gynechiatry”, an original word which he has coined. For reading the manuscript and offering many suggestions, the author is indebted to Doctor Douglas Haynes, Doctor William Christopherson and Doctor Harold Gordon. Doctor Malcolm Barnes has been most helpful in the selection of material for illustrations. I am most indebted to Mrs. Jean Hellstrom for her long and patient efforts to demonstrate the pathological lesions in her tone drawings. The photomicrographs have been prepared with great care by Mr. Wendell Gillette. As always, my loyal secretary, Mrs. Phyllis Ray, has been of inestimable aid in the preparation of this book.

The drawings illustrating vaginal hysterectomy are from the first edition of the author’s book “Vaginal Hysterectomy.” The drawings illustrating abdominal total hysterectomy by the author are presented by permission of the editor of the American Journal of Obstetrics and Gynecology.

L. A. G.

Contents

Chapter I

Page
Preface vii

Acknowledgments ix

THE PATIENT PRESENTS HERSELF 3
- The History 4
- Gynecological Examination 6
- Impression 15
- Disposition 15

Chapter II

HORMONES IN GYNECOLOGY 16
- Hypothalamus 16
- Pituitary Gland 17
- The Ovary 20
- Estrogens for Clinical Use 25
- Progesterone for Clinical Use 29
- The Adrenal Gland 30
- The Thyroid Gland 33
- Androgens in Gynecology 34
- Assay of Hormones 35

Chapter III

DISEASES OF THE VULVA 40
- Venereal Diseases 40
- Non-venereal Infections 57
- Neurogenic Diseases 61
- Trophic Diseases 61
- Other Precancerous Lesions 69
- Tumors of the Vulva 71

Chapter IV

DISEASES OF THE VAGINA AND FEMALE URETHRA 79
- Inflammations of Vagina 79
  - Prepubertal vaginitis 79
  - Vaginitis during menstrual life 83
  - Post-menopausal vaginitis 89
- Tumors of Vagina 90

Page

Lesions of Female Urethra 94
Caruncle 95
Diverticulum 97
Carcinoma 101

Chapter V

THE UTERINE CERVIX 106
Acute cervicitis 108
Chronic cervicitis 109
Chronic cystic cervicitis 111
Endocercivitis 113
Lacerated cervix 115
Cervical stricture 116
Cervical polyp 117
Squamous metaplasia 119
Basal cell hyperplasia 120
Bowen's disease 120
Dysplasia 120
Carcinoma of cervix 134

Chapter VI

ENDOMETRIUM, MENSTRUAL FUNCTIONS AND DYSFUNCTIONS, NEOPLASMS 160
Menstruation 160
Changes with menstruation 165
Anovulatory menstruation 167
Hypomenorrhea 167
Oligomenorrhea 167
Primary amenorrhea 168
Secondary amenorrhea 169
Metrorrhagia 171
Menorrhagia 175
Dysmenorrhea 177
Adenocarcinoma 178
Carcinoma-in-situ 189

Chapter VII

DISEASES OF THE MYOMETRIUM 198
Myomas of uterus 198
Adenomyosis 209
Subinvolution 212
Fibrosis 214
Pelvic congestion 215
Sarcoma 217
Mixed mesodermal tumors 222

Page

- Stromal myosis 223
- Indications for hysterectomy 225
- Technique of abdominal hysterectomy 232
- Technique of vaginal hysterectomy 239

Chapter VIII

THE FALLOPIAN TUBES 246

- Salpingitis 247
- Post-abortal and post-delivery salpingitis 257
- Post-appendicitis salpingitis 259
- Tuberculous salpingitis 260
- Ectopic pregnancy 267
- Carcinoma 278

Chapter IX

DISEASES OF THE OVARY 282

- Functional diseases 282
- Inflammatory diseases 291
- Endometriosis ovary 292
- Tumors 294
  - Serous cyst 295
  - Papillary serous cystadenoma 296
  - Papillary serous cystadenocarcinoma 299
  - Pseudomucinous cyst 305
  - Pseudomucinous cystadenocarcinoma 308
  - Primary solid adenocarcinoma 308
  - Secondary carcinoma 310
  - Dysontogenetic tumors 313
  - Other masculinizing tumors 322
  - Non-hormone secreting tumors of developmental origin 322
  - Fibroma 325
  - Sarcoma 325
- General symptomatology and diagnosis of carcinoma 327
- Clinical consideration of carcinoma of ovary 330
- Chemotherapy of cancer 331

Chapter X

ENDOMETRIOSIS 335

- Definition 335
- Theories of origin 337
  - Müllerian duct 337
  - Retrograde menstruation 337
  - Ivanoff-Meyer serosal theory 337
  - Lymphatic metastases 338

Page
Blood stream metastases 338
Adenomyosis 339
External endometriosis 342
Diagnosis 352
Treatment 354

Chapter XI

RELAXATIONS AND DISPLACEMENTS, FISTULAS 363
Relaxed vaginal outlet and rectocele 363
Cystocele 364
Prolapse of the uterus 366
Incontinence of urine 372
Malposition of the uterus 375
Acute anteflexion 375
Retrodisplacement 377
Vesico-vaginal, vesico-cervico-vaginal, and uretero-vaginal fistulas 384
Recto-vaginal fistula 390

Chapter XII

DISEASES OF THE PLACENTA AND EARLY PREGNANCY 394
Diseases of the placenta during the first trimester 394
Abortion 395
Hydatidiform mole 399
Chorioma destruens 404
Chorion epithelioma 406
Diseases of the placenta and pregnancy in the mid-trimester 408
Diseases of the placenta in late pregnancy 409

Chapter XIII

HERMAPHRODITISM AND CONGENITAL ABNORMALITIES 411
Hermaphroditism 411
Chromosomal sex 412
Gonadal sex 413
Body sex 413
Adrenal hyperplasia 417
Adrenal tumors 417
Arrhenoblastoma 417
Müllerian duct abnormalities 419
Urogenital sinus abnormalities 419

Chapter XIV

STERILITY 435
Organic abnormalities 435
Functional or endocrine abnormalities 438

Page
Psychogenic factors 439
Male factors 440
Investigation and treatment
Female 440
Investigation and treatment
Male 444
Artificial Insemination 445

Chapter XV

MENOPAUSE 447
Definition 447
Symptoms 447
Treatment 448
Effects of estrogen on genital tissues 450
Duration of symptoms and therapy 451

Chapter XVI

GYNECHIATRY 453
Virginity 453
Frigidity 454
Sexual compatibility 455
Obesity 456
Post-partum psychosis 456
Sexual deviation 456
Sex instruction 457
Premarital counselling 457
Psychosis 457

Index 459

A TEXTBOOK OF
GYNECOLOGY

CHAPTER I

The Patient Presents Herself

Every woman should have regular, periodic pelvic examinations. For that matter, every person, man or woman, should have regular physical examinations. But such a goal, while most desirable, must await the millenium. On the other hand, there is a definite increase in interest in these routine procedures in the examination of women, stimulated greatly by the newspapers and magazines, and by various lay-medical organizations, such as the American Cancer Society, and the many other groups, which are banded together for their own particular medical interests. As the value of the Papanicolaou cytology test becomes more obvious, and the medical profession becomes more keenly aware of its accuracy, another great stimulus will have been added for regular pelvic examination. Lay knowledge and interest will progress and continue, and undoubtedly more and more women will present themselves for routine examinations.

The majority of women who present themselves to the gynecologist, or general practitioner, or internist, for pelvic examination are married, have children, and have developed some pelvic complaint, whether related to minor functional disturbances or to serious disease. These mothers may bring in their small daughters with pre-pubertal vaginitis, their children at puberty with delayed menses or abnormal bleeding, their adolescent daughters with dysmenorrhea, or the young women who sincerely desire, or have been advised to seek, premarital advice. Similarly, these active and mature women may bring in their elders, their mothers, aunts and grandmothers, who complain of nervousness, vaginal irritations, pruritus, abnormal bleeding, prolapse, or abdominal enlargements. A certain proportion of patients is made up of divorcees, who realize the importance of their femininity and sex, because this has been brought home to them after their dramatic separations from their mates, and who are more cognizant of the necessity of maintaining their health. The busy mother may neglect herself, caring not only for her brood, but for her sometimes tense, egocentric and demanding husband. As knowledge of the Papanicolaou test is more widely disseminated, more and more women of all ages request this examination. Many of these patients must have the explanation that the cytology test is essentially only a test for the cervix uteri and that it does not replace careful pelvic examination. The information obtained from cytology, while accurate, largely relates to neoplasia of the cervix alone.

As the patient presents herself, there is always a sense of some reluctance, modesty, and nervousness, combined with some anxiety as to the verdict of the examination. Similar tensions undoubtedly affect the majority of men when they have physical examinations, but it appears that the emotions of the woman are more sensitive, more near the surface, and more intense. It is important that the receptionist, the secretary and the nurse, be courteous and friendly. They should exhibit a professionally interested manner. These contacts aid much in maintaining a woman's confidence, understanding and emotional ability to accept a diagnosis, carry out directions, and have performed necessary procedures without emotional upheavals.

When the patient meets her physician, she responds to a genuine warmth of human interest, and is given confidence by a maintained courteous professional manner. While friendliness is to be developed, familiarity often leads to loss of confidence or lack of appreciation of serious opinions.

THE HISTORY

In the practice of gynecology, it is important to obtain a concise, accurate and encompassing history of the patient's background and her illness. This should be standardized, so as to expedite the method of obtaining the record, and in order not to miss important points. Ordinarily, the gynecologist takes his history form from that which he has learned in the study of internal medicine, but he shortens and abbreviates his form and method, so as to touch on the high points, to explore each system briefly, and to determine if any area should be investigated more thoroughly. Some clinicians have preferred to use small cards on which the systems and complaints are printed. A positive or negative finding may be checked. Others use a printed form, enumerating the systems and some points under each which may prompt queries. Details are supplied in each individual case. It is important to elicit those symptoms that may be related to any positive findings in the examination, in order to evaluate the patient properly. Listing all symptoms originally is important in retrospect after treatment, to clarify non-related and pre-existing complaints. This latter point may seem unimportant, but time reiterates its usefulness. The patient may misunderstand what is to be expected, regardless of repeated previous explanations.

In the history of the patient, the first question always is related to the *chief complaint*. This must be distinctly enunciated, as clearly as possible. Ordinarily, in gynecology, commonly this has some relation to menstrual dysfunction, to pelvic pain, or to discharge and irritation. A certain percentage of patients have no complaint, but wish a routine examination, particularly to exclude malignancies. Often, patients, in considerable number, complain only of nervousness, which at first is vague and indefinite, with perhaps many associated symptoms.

The family history is rarely entered into by the gynecologist. While malignancy may have some familial and congenital association, and in fact it undoubtedly does, this is of no great importance in determining the diagnosis and treatment of any individual patient. The inherited diseases in gynecology are so rare as to be of little importance. That nervousness is familial and inherited is undoubtedly correct, to a certain extent. But the exact situation with the individual patient is the important matter.

The *past history* begins with a statement regarding the *general health* of the patient. The *energy status,* whether normal, low, or excessive is an important general question, having some bearing on the thyroid activity and nervous tension of the patient. *Serious illnesses* are enumerated, because of possible relation to the general resistance and gynecologic system. *Operations* particularly must be listed specifically along with their dates. This information may indicate absence of the appendix, or the presence or absence of fallopian tubes, etc., and may influence greatly the subsequent diagnosis and operative treatment. *Cardio-respiratory* symptoms are inquired into, including chest pain, precordial pain, palpitation, dyspnea, edema, cough, breathlessness. Any positive answer is to be explored further, as indicated. *Gastro-intestinal* symptoms may include abdominal pain, nausea, vomiting, constipation, diarrhea and indigestion. The character of any of these symptoms should be elucidated in some detail. The type of abdominal pain is accurately described as to its occurrence, severity, character (continuous, intermittent, cramp-like), localization and moveability. The physician must consider in his evaluation of the history the indication for specific tests and detailed investigations of any system. The patient is questioned as to frequency of *urination*, nocturia, pain, burning, stress incontinence, or urgency incontinence (the differentiation of the latter two being important in regard to relaxation of vesical muscles and fascias, as contrasted with irritation in the urethra and bladder).

The *menses* are described in detail, including the time of onset (menarche), the cycle with its approximate number of days and variations, the duration of flow, the amount of flow (scant, moderate, heavy), the presence of clots, and the occurrence of dysmenorrhea. The character of the pain is determined, whether it is constant, localizing in the midline or sides or rectal areas, whether it is cramp-like or continuous in character, or whether it represents some strange type of discomfort, as burning or weakness or pressure. *Intermenstrual bleeding* (I. M. B.) is a most important symptom, and its time of occurrence must be noted carefully. It may represent the dwindling of a menstrual period, the prodromal signs of menstruation, or bleeding associated with ovulation. One must not be led astray from the fact that any abnormal bleeding may represent a malignant tumor. Careful questioning is necessary in relation to the occasion when irregular bleeding occurs, its quality and relation to activities, particularly sexual intercourse. *Discharge* is one of the most frequent symptoms of which women complain. The amount of discharge and its relation to menstruation, whether occurring immediately before or immediately after, at the time of ovulation, or continuously between menses, are to be recorded, along with a description of its odor and color (clear, white, yellow, brown or green). The presence of blood in discharge is to be carefully distinguished.

The next and an important question is the date of the *last menstrual period.* This is of particular importance because the majority of women are susceptible to pregnancy; certainly menstruating women are. Pregnancy may occur in the most unexpected and inopportune situations, which may be dissembled as carefully as possible from the families involved and the physician. At times, a patient is completely unsuspecting herself, particularly because a pregnancy may be entirely unwanted, and even a tragic accident. The differentiation of many pelvic tumors from pregnancy is of greatest importance. While the date of the last menstrual period is never conclusive in the diagnosis, it is of importance and another link that adds to an accurate diagnosis. The author had this point indelibly impressed upon his mind many years ago. During a third year class in Gynecology under the late Doctor Thomas S. Cullen, at an operative clinic given for small groups, the author narrated the history of the anesthetized patient being prepared for abdominal operation. As the history unfolded and seemed complete, Doctor Cullen asked what item had been omitted. Since everything was thought complete, he asked the date of the last menstrual period. With consternation the written history was re-examined, and no date was recorded. Doctor Cullen then pointed out that this was a symmetrical mass in the lower abdomen, that while he thought pregnancy was not present, he considered it a serious dereliction to operate without at least having known the date of the last menstrual period. This student was instructed to return with the anesthetized and unoperated patient to the ward, and remain at her bedside until she was sufficiently coherent to give an accurate answer. Doctor Cullen made much of this incident, proclaimed a fine of twenty dollars against the student to be paid to the class (which was never collected!), and subsequently removed the myomatous uterus at a later session. The number of *pregnancies, the* number of *abortions,* and *difficulties with deliveries,* including fevers, hemorrhage, the use of forceps, and previous emergency procedures, are enumerated. The *weight* of the patient, present and past, with gains and losses, is to be noted.

The *present illness* is recorded as a relatively short but accurate summary of the patient's true complaints, and includes all of the reasons which brought her to the physician. Abnormal bleeding, whether prolonged, profuse, irregular, or intermenstrual bleeding, constitutes a large percentage of primary gynecologic complaints. The frequency of occurrence and the duration of this complaint must be determined accurately. Pain is another frequent complaint that brings the woman to the physician. The type, its location, duration, moveability, and radiation to back, flank, groin, thighs or rectum, are to be carefully distinguished. A third common complaint is discharge; it is described briefly, as to its duration, severity, type, color, and association with burning, pain or pruritus. The next large group of women comes to the gynecologist with the complaint of nervousness, which may or may not be associated with hot flashes. A patient with chief complaint of nervousness, may be of menopausal age, postmenopausal, or quite young. Evidently very many women think nervousness is related to their ovaries and hormones. The occurrence of hot flashes with normal and regular menstruation is a frequent one, and yet, hot flashes can never be of menopausal origin if the patient is menstruating, because the presence of a normal amount of estrogen, necessary for menstruation, cannot possibly allow hot flashes of menopausal origin; these hot flashes are due to nervousness or anxiety. If the nervousness and hot flashes are possibly menopausal, the cessation of menses is carefully documented. Other patients complain of tumors, or prolapses, or swellings, which are caused by distinct pathological entities, or which may be caused by weight gain, or may be phantom. Still other patients have no complaints, but simply want the cancer smear test and routine examination. Others have very vague complaints, and it may seem difficult to find just why the patient did present herself. Usually after the examination of the latter has been complete, if the patient has been given another opportunity to elucidate, then her family troubles, sex difficulties, frigidity, or her husband's infidelities are poured out with tears. It is particularly important to encourage patients to ask questions, and to add to their history after the examination has been completed, and a professional opinion has been expressed. Often many emotional problems with direct relationship and previous methods of treatment now are explained by the patient.

GYNECOLOGICAL EXAMINATION

The *gynecological examination* should include an overall survey of the patient. The relation of every system to the reproductive is well known. For this reason all patients are asked to remove their clothing completely, and after voiding (and the specimen is given immediate routine analysis), the patient may be draped with sheet (half size or cot size) on the table with feet in stirrups. Shoes may remain in place for comfort and convenience. A small hand towel may be placed across the breasts.

First, a notation is made of the *general appearance,* as to whether the patient is normally nourished, obese, underweight, healthy-appearing or ill-appearing. The mucous membranes are carefully inspected, which allows one an opinion of the hemoglobin content. This evaluation is made by observing the conjunctiva and the tongue. Inspection of the nail beds is helpful, if tinted polish has not been applied. The face and body are inspected for abnormal hair. At the same time the presence of any *skin lesions* are noted. These are important, because lichen planus, psoriasis, lichen sclerosis et atrophicus, and generalized skin diseases may have primary symptoms limited to the vulva. The incidental finding of skin cancers and suspicious pigmented moles may aid the patient in another direction. The *thyroid* is carefully palpated, because thyroid function is intimately associated with genital function. Hypothroidism, which has the more important ovarian effects, usually is not associated with an enlarged gland. Diffuse enlargement may represent the colloid goitre without symptoms, or the marked hyperplasia with hyperthyroidism. The nodule, when present, may produce no symptoms, or may produce nervous and toxic complaints. At the same time the texture of the skin of the body is noted, because of its relation to thyroid function.

The *breasts* are examined and described as to size, shape, pendulous appearance, softness, firmness, and presence of areas of thickening. The latter occur especially in the upper outer quadrants. Particularly, one must distinguish between the round, slightly fluctuant or tense cysts, of which the small ones may feel like B-B shots, while the larger ones may be more distinct and measure up to several centimeters in diameter. These are to be distinguished from the hard, discrete tumor mass, with sharp little barbs palpable around its surface, with a tendency to pull the skin in to the tumor from shortening of the connective tissue between the breasts and skin (Cooper's ligament), or with degrees of attachment to the chest wall, if more deeply placed. The breasts are best palpated with the fingers flat, moving them over the breast tissue in sequence, as though playing the piano. This simile was made years ago by Bloodgood. The flat ball-part of the fingers more readily discriminates masses. Very careful but gentle palpation of every part of the breast is necessary. If there is any question at all, examination in the sitting position determines the equality of the nipples and their positions, and retraction of the skin may be observed more readily under oblique light. As the patient bends forward, allowing the breasts to fall away from the chest wall, irregularities and dimpling may be seen. The patient's own opinion as to location of a mass is quite important. The presence of any small, hard nodule indicates prompt excision and frozen section examination. More frequently, the suspected area of tumor is less definite and seems to represent an area of thickening. Indefinite tumors are observed over a period of one month or longer, as seems proper, because many of these areas completely disappear in subsequent cycles, or vary so much in size and shape as to represent obvious changes from ovarian hormones. The presence of one or more obvious cysts of the breast of any size indicates aspiration. A twenty-two gauge needle is passed into the interior of the cyst, the fluid completely aspirated and sent to the laboratory for Papanicolaou cytology studies. Cysts are rarely malignant. Occasionally they may contain papillomas on the interior which are usually benign, but a few do represent papillary cystadenocarcinomas. On occasion, a thickened area in the wall of a cyst may represent a separate, malignant growth. Ordinarily, the aspiration of cysts should be performed by the surgeon who is prepared to perform indicated breast surgery, if cytologic studies show abnormal cells, or if aspiration gives no fluid and the tumor is apparently solid.

The *heart and lungs* are checked briefly, and the *blood pressure* is recorded. This is not considered a thorough and complete cardiovascular examination, but it does permit an opinion of the patient's stamina and any obvious disabilities. The *pulse rate* is noted accurately, as the rate may be related to thyroid function.

The *abdomen* is examined, including thickness of the wall, degree of obesity, weakness and separation of muscles, operative scars and their firmness or weakness, and areas of tenderness, with radiation and degree. The size, consistency and any tenderness of the liver, kidneys and spleen are determined. The presence of any mass, whether behind the symphysis or in any part of the abdomen is described carefully. The sigmoid and cecum are palpated, and the presence of spasm or mass in those areas is noted. Rigidity and rebound tenderness are studied in detail, especially if the symptoms are recent and acute. The inguinal, femoral, umbilical and upper midline areas are palpated for the presence of hernias; if any are suspected, these areas are examined in the standing position, and after cough and straining.

The *pelvic examination* first includes inspection and palpation of the vulva, with search for any hypertrophic, edematous, elongated, atrophic and shrunken portions of this special skin, or areas of thickening and ulceration. Elongations of the minora may be related to manual stretching or may be of congenital origin. Small furuncles in the hair are common; sebaceous cysts and various types of tumors are noted. The clitoris is inspected, with particular regard to its size, prepuce, and adhesions or inflammation. The vestibule should have a homogeneous pinkish-gray appearance. The status of the hymen, as to whether it admits a digit or more, is noted. The Bartholin's glands are palpated by the thumb and forefinger as they are deeply placed in the labia majora at the level of the middle of the vaginal orifice. The normal gland is not palpable. Chronic inflammation may be indicated by the presence of a thickened pea or bean-sized nodule, or a cyst from one to several centimeters in size, caused by occlusion of the duct from inflammation. Beneath any cyst that is present, usually definite thickening in the gland may be felt, caused by chronic inflammation. The acute abscess, with its swelling, induration or fluctuation, shows redness, edema, and extreme pain and tenderness, and is obvious from the patient's complaints and superficial examination.

The *urethra* is inspected for caruncle and discharge. It is milked by pressing the urethra against the symphysis pubis, withdrawing the finger to determine secretion in the urethra, and especially from the Skene's ducts, which may be seen as minute pits on each side of the posterior meatus. Redness around the urethra, caruncle in younger women, and some redness around the vestibule, often indicates the presence of trichomonas.

Before palpating the vagina further, a clean and dry speculum is inserted. The proper size must be determined by the appearance of the orifice. Sometimes there is difficulty in exposing the cervix, especially if there are malpositions of the uterus or tumors that distort the vaginal canal. When the *cervix* is exposed, the Papanicolaou cytology preparations are taken on two slides, the first with small applicator with tip of non-absorbent cotton, which extends up into the cervical canal. The non-absorbent cotton absorbs fewer of the cells into the interior of the swab. The swab is then rolled on to the clean slide and *immediately* immersed in the solution of fifty per cent alcohol and fifty per cent ether. Then the Ayre wooden spatula, modified from the tongue blade to extend into the cervical os, is inserted, spun around the cervical os, and gently wiped on the second clean slide, which again immediately is placed in the fixing solution.

The Papanicolaou smear test, or cytology examination, is of extreme importance. No pelvic examination is complete without this cytology study. It is unfortunate that such a small percentage of women can have this test performed accurately at the present time. Probably less than ten per cent of women have this facility available. The reason is the paucity of skilled technicians. Certainly the physician-pathologists are not able to examine the smears of all women. It is remarkable that a properly trained

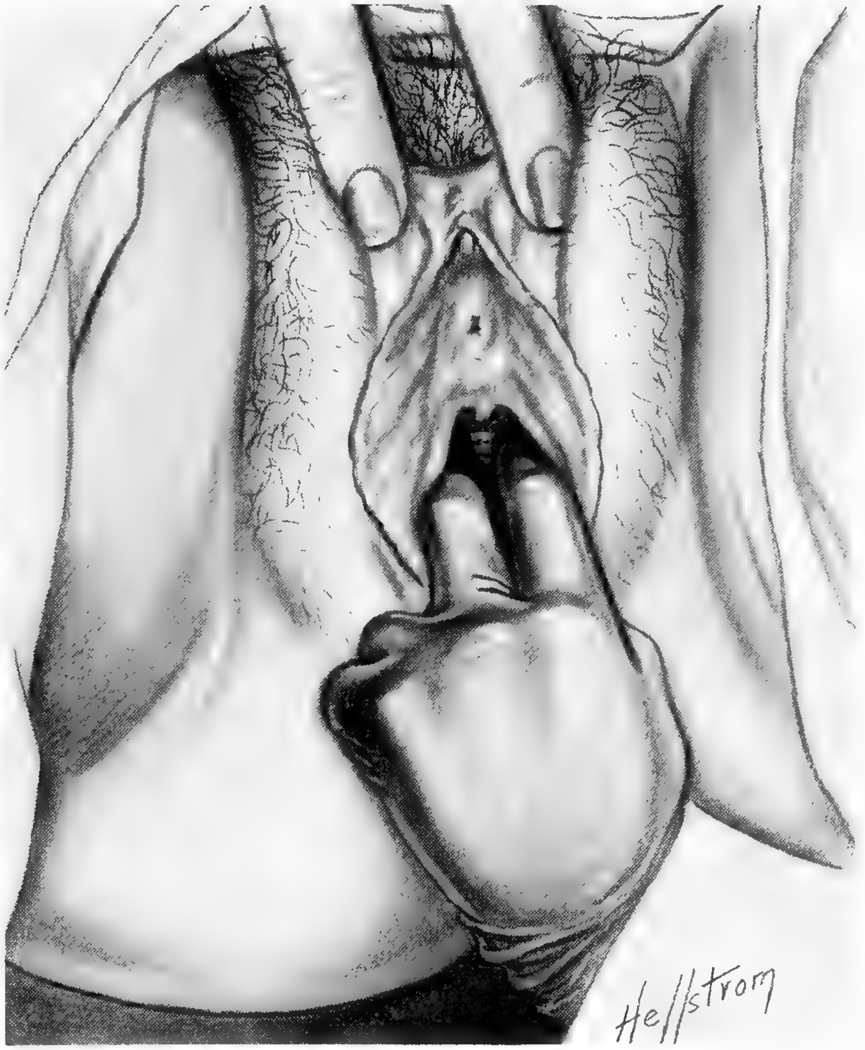

Fig. 1. Pelvic examination. The external genitalia are carefully inspected. This includes development, hair growth, thickness of the skin (normal, thinning, atrophy, leucoplakia, lichenfication), inflammation, cysts, tumors, ulcerations, moles. The clitoris, prepuce, sebaceous glands of the labia, and Bartholin's glands are noted carefully.

The dry speculum is inserted into the vagina to expose the cervix. The Papanicolaou smears are made by inserting the small swab tipped with non-absorbent cotton up into the cervical canal. The Ayre spatula then scrapes the cervix for the second slide. A fresh preparation then is made after withdrawing the speculum, washings of the vagina are taken with the medicine dropper containing normal saline.

Holding the labia apart, the two lubricated gloved fingers are inserted gently, to palpate the Bartholin's glands against the thumb, then turned, separated, and pressed posteriorly to test the support of the perineal outlet. The patient voluntarily constricts her muscles, and also strains to demonstrate any cystocele or rectocele. The character of the mucosa and vaginal inflammations become evident.

technician may develop such a degree of proficiency in the detection of abnormal cells. One does not ask the technician to make a definite diagnosis, but simply to screen out those who may need further study. One of the great needs of the country is the training of many more of these technicians and their placement at all strategic points, so that physicians may make these smears and have them read accurately. As these technicians become available (under guidance of the pathologist, of course), the physician must be convinced of the necessity of the routine use of the smear test, after which every patient must be educated to the necessity of having the test performed.

After the speculum is withdrawn, *washings* of the vagina in normal saline are taken with the medicine dropper, and a drop is placed under a cover slip. This fresh preparation is made before any lubricating jellies are applied, or further palpation is performed. Microscopic examination quickly reveals four important points: (1) the epithelial cells are large, hexagonal with small nuclei, if there is a full estrogenic effect, and tend to be curled if progesterone also is present in the last half of the cycle. The epithelial cells are small, round or oval, with relatively large nuclei, representing the basal or parabasal cells, if the vagina is thin and estrogens are absent. All degreees of in-between variations may be seen. The round and oval cells are seen in the true menopause, but are found not infrequently the last day of menstruation, or a day or two thereafter, when the blood level of estrogens is quite low. (2) The presence or absence of pus cells determine immediately whether or not inflammation in the vagina or cervix is present, although just before menstruation, polymorphonuclear leucocytes are exuded from the endometrium. As a rule, one readily determines the presence or absence of vaginitis or cervicitis, and differentiates the eversion without inflammation from eversive cervicitis. (3) The presence of trichomonas vaginalis usually may be determined quickly, although at times prolonged search is necessary. (4) The presence of fungi is indicated as transparent mycelia with their typical buds, often enmeshed in epithelial cells. Prolonged search may be necessary to reveal these elusive organisms.

The appearance of the cervix and walls of the vagina have been kept in mind, as seen at the time the cytology slides were prepared.

Palpation is the next phase of the examination. The question of which hand to use for internal palpation will never be agreed upon, because strong proponents of each will always exist. Certainly it is better to use the same hand each time, as the sensitivity increases remarkably with practice. Few are so ambidextrous as to use either hand. Probably the majority use the right hand, because, being dominant, it has been more agile and adept at palpation before this study. Most obstetricians seem to prefer the accuracy of their right forefinger in rectal examination, and their two first fingers of the right hand for pelvic examination. There are some who continue to prefer the method of Kelly, using the left hand routinely. There is no doubt that the left forefinger and middle finger may develop remarkable sensitivity with frequent use. Placing these fingers in the vagina, standing not in front but to the side of the patient, they are used rather passively, the right hand sweeping the organs deeper into the pelvis by stronger though careful pressure on the abdominal wall. At other times, during pelvic surgery, if one operates from the patient's right side, the more sensitive left hand may be used to make blunt dissections in the depth of the pelvis, beginning from the midline posterior to the uterus, and extending laterally. Also the left hand may be used to incise and suture against, using its sensitiveness to protect other and vital structures. The main point is the use of one hand routinely, to develop sensitiveness in the finger tips.

The *outlet* of the vagina is then palpated to determine its muscular tone, degrees of relaxation and stenosis or narrowing. The patient is asked to strain, or bear down, to determine relaxation of the anterior or posterior vaginal walls, which may represent a cystocele or rectocele. Contractility and tone of the vaginal muscles are important, because lack of strength in the muscles seems a factor in future relaxations and in the development of stress incontinence. The thickness of the vaginal mucosa and the presence of rugae are noted. Cysts in the lateral walls, derived from Gartner's ducts, the congenital remnant of the lower wolffian duct system, may be palpated, though not visualized in earlier inspection. Suburethral diverticula and cysts, and subvesical cysts, are palpated occasionally. Small hard nodules, one cm. or less in diameter, beneath the lateral walls, are considered fibrosed or calcified lymph nodes. Septate vaginas may be obvious or occasionally occult, the septum deviating readily to one side, separating either a normal or rudimentary canal.

The position of the *cervix* is noted, as to its location in the normal position, or lower, or higher, or deviated to one side. The cervix may point in the normal direction across the vagina, or may point sharply

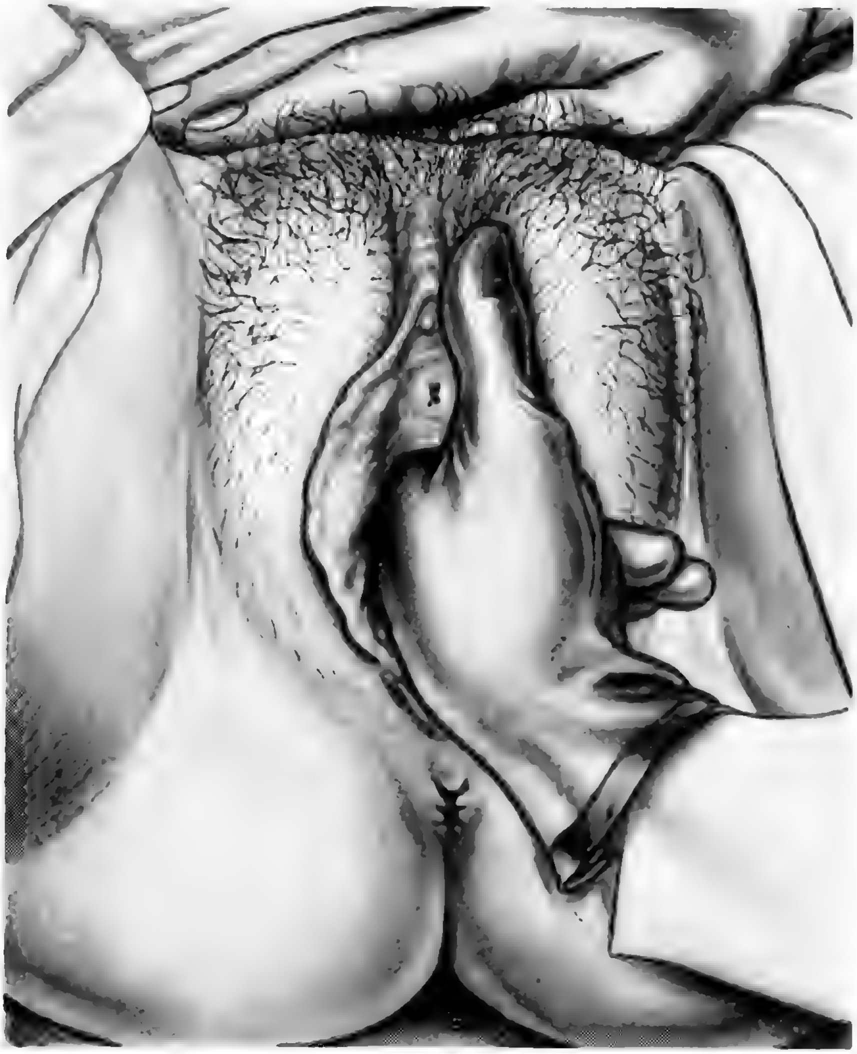

Fig. 2. Internal examination consists of palpation of the vagina, the cervix, ballotment and palpation of the corpus with the abdominal hand, and exploration of the fornices and adnexal regions and cul-de-sac. The gentle examination, obtaining the patient's confidence, and the encouragement of her relaxed attitude and abdominal muscles are necessary for the best examination. The rough and rapid examination may cause so much discomfort and voluntary muscle spasm as to prevent obtaining nearly as much information as the gentle and unhurried approach. The abdominal hand sweeps the ovaries into the pelvis, when the patient relaxes her muscles. Finally, rectovaginal examination, with middle finger in the rectum and forefinger in the vagina, gives information regarding hemorrhoids, fissures, sphincter tone, fistulous openings, strictures, character of the rectal mucosa and rectovaginal septum, and finally the cul-de-sac, uterosacral ligaments, ovaries and pelvic tumors.

posteriorly or anteriorly towards the symphysis. Some tumors may displace it in most inaccessible locations. The cervix is palpated carefully, and notation is made of its size, shape, consistency (soft, rubbery, or hard), the presence of follicle cysts, from a few millimeters up to two centimeters in diameter, and granulations in erosions or eversions of the cervix. The latter usually are fairly readily distinguished by the sensitive fingertip through the rubber glove. The character of the cervical os is of importance, including a soft, rubbery or hard consistency, and a constriction of the os or a dilatation of the opening, which may admit the finger or finger tip. The striae of the dilated endocervix and the presence of irregularities and polyps may be determined by the delicately trained finger. In the record, the appearance of the cervix is then described including the presence of eversion, ulceration, cysts, polyps, leukoplakia, bleeding from touch, lacerations and granulations.

The *corpus of the uterus* is palpated, the two vaginal fingers being placed under the cervix, the abdominal hand being used to feel the corpus. By pressing up and down with fingers in the vagina, the hand on the abdomen is able to determine the outline of the fundus, and the size, consistency, irregularities and moveability of the corpus. If the abdomen is obese, or if the patient cannot relax her abdominal muscles, palpation of the uterus may be impossible, or at least, the information obtained may be sketchy, to say the least. If the uterus is retrodisplaced, the abdominal hand determines the absence of a mass in the anterior portion of the pelvic cavity. Information as to the size and shape of the retrodisplaced uterus is determined only by the fingers in the vagina which are passed up behind the cervix, to each side and in front of the cervix. While the apex of the uterus in such a position cannot be palpated, an estimate of the size is made by the direction in which the examining fingers seem to extend. It is important to determine the mobility of the uterus. If it cannot be elevated, the posterior surface of the uterus is assumed to be adherent (though often it only seems immoveable, and really is not adherent). The ability to elevate the uterus depends on the relaxation of the patient's muscles, the depth of the pelvis and the fulcrum of the cervical ligaments. Usually, if possible and not too painful, the retroverted uterus is raised to anterior position in order to determine its mobility, and its size, shape and consistency.

The size of the uterus must be estimated. The infantile uterus is not only quite small, but has a corpus of similar size or even shorter than the cervix. The hypodeveloped uterus is small, particularly narrow, and may even be elongated. The normally small pubertal and adolescent type of uterus is interpreted in accordance with the patient's age. The enlarged uterus, one and one-half to two times normal size, may represent a normal variation in the menstrual cycle. Occasionally a uterus is suprisingly large immediately before menstruation. But more often, the enlarged uterus is permanent; it may be due to subinvolution, fibrosis, adenomyosis, or myomas. Nodules projecting from the surface of the uterus are carefully described, in order to provide accurate observation at subsequent examination.

After a careful consideration of the uterus, and its normal or abnormal findings, the forefinger and middle finger are placed in the left fornix of the vagina, lateral to the cervix, and elevated to a moderate degree. Then, with the right hand on the abdomen, a sweeping motion is used to press the ovary deep into the pelvis. After three or four gentle sweeping motions, attempting to gain the patient's confidence and have her continue relaxation of the abdominal muscles, the hand is pressed deeply into the abdomen and held. Then the fingers in the vagina are moved about, back and forth and side to side, to find the ovary. In a majority of patients this ovary may be felt, without anesthesia, particularly if the patient is cooperative and can relax the abdominal mus-

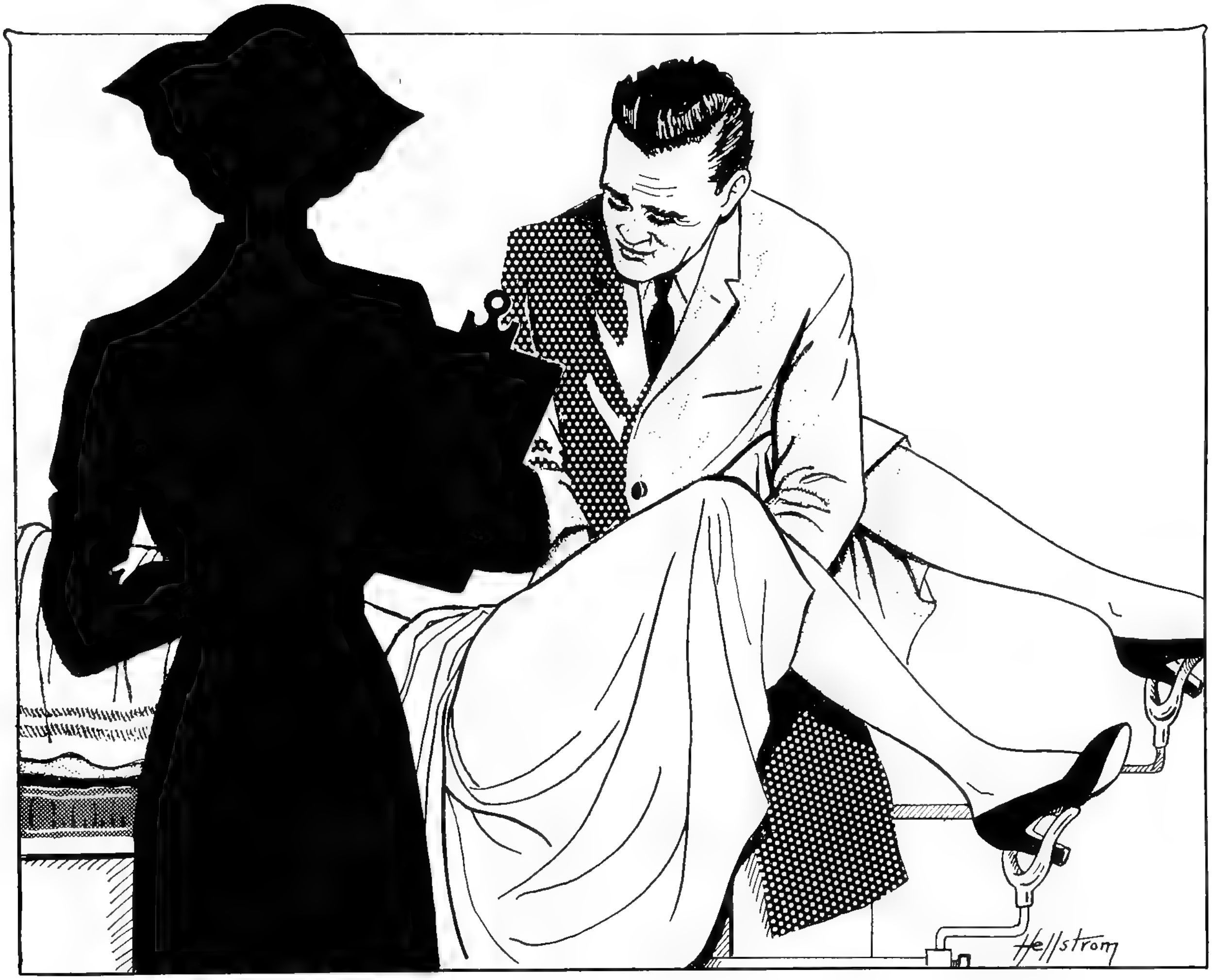

Fig. 3. If the examiner stands to the side of the patient, the pelvic organs, including the ovaries, may be felt more readily. As a rule the same hand is used for every internal examination. The sensitivity of the finger-tips increases with use.

At all times, the patient must be properly draped. The presence of the nurse as assistant and chaperone is emphasized.

cles. The normal ovary, with its three by five centimeter or smaller size, is quite mobile, slipping quickly away from the vaginal fingers, and is rarely felt by the abdominal hand. The determination of its size may come from only the momentary palpation of the underside of the ovary. From this, one must construct in imagination the apparent size of the ovary. Small cysts may represent benign physiologic follicular or luteal cysts. The cystic tumor of large size, whether the dermoid, serous, pseudomucinous or malignant cyst, and the large solid tumors may be palpated by the hand on the abdomen.

Discussion of the fallopian tube has been omitted so far. The reason is that the normal fallopian tube is small, soft and impalpable as a rule. Perhaps it may be felt in the extremely rare case, but this is never a dependable palpatory finding. In the case with acute salpingitis, again the tube is not palpable. In subacute salpingitis, the tube is enlarged to form a pyosalpinx, and may become adherent to the ovary and form a tubo-ovarian abscess. The subacute infection is associated with induration in the broad and uterosacral ligaments. This induration is characteristic of subacute inflammation. In the chronic stage of salpingitis, the induration has disappeared, and there may remain the hydrosalpinx, palpable as a soft sausage-shaped mass, or the tubo-ovarian inflammatory cyst, an adherent cystic mass. As the inflammation recedes in the chronic state, the tube itself may be impalpable, and the diagnostic palpatory finding of chronic tubal inflammation remains as the adherent ovary. In the acute phase of salpingitis, sticky pus drips from the end of the tube over the ovary. Soft fresh adhesions form, which become firm and remain long after any acute or subacute inflammation has been absorbed. Palpation of the ovary in the patient with chronic salpingitis reveals that it is fixed, or only slightly moveable. This means that long ago there has been acute inflammation in this pelvis, and that chronic salpingitis may be diagnosed at this time. The cystic adnexal mass, when adherent, indicates the presence of a tubo-ovarian inflammatory cyst, an endometrial cyst or a malignant cyst. These must be distinguished if possible by further history, from the examination, and careful follow-up of the patient.

The "velvety" mass (Cullen) to the side of the uterus may mean the presence of a tubal or ectopic pregnancy. Here again the history of the patient is most important in the index of suspicion of diagnosis; otherwise the "velvety" mass may represent a soft temporary ovarian cyst, a hydrosalpinx, or only an intestinal loop containing liquid fecal material and gas. The posterior fornix of the vagina is carefully palpated, to discover in the cul-de-sac of Douglas the presence of any thickening, induration or shotty nodules, representing endometriosis, inflammatory reaction or tumors. The earliest forms of endometriosis appear as the very small irregular nodules, as though containing spicules, on the surface of the uterosacral ligaments. The B-B shot nodules in the cul-de-sac are characteristic of this disease. They represent endometrial implants with surrounding fibrous tissue reaction. These small shotty nodules are extremely tender. It is to be noted that often the normal cul-de-sac of Douglas may be quite tender to palpation. Other indurations in the cul-de-sac may represent carcinoma, metastatic from the ovary or stomach or other areas of the abdominal cavity; this is always to be considered. The retroverted uterus, adherent and tender, associated with shotty nodules in the cul-de-sac and induration in the uterosacral ligaments make a characteristic and frequent combination; usually the patient complains of dysmenorrhea, dyspareunia and sterility.

In the patient who has the symptoms of bearing down, pressure and fallen sensation in the pelvis, and who has an unusually mobile uterus, a tenaculum is placed on the cervix to determine the degree of prolapse.

As a part of the regular pelvic examination, the middle finger is inserted into the anus and rectum, noting carefully the presence of external and internal hemorrhoids, the presence of fissures which are often palpable, the orifice of an anal fistula, the sphincter tone, and the character of the rectal mucosa. Any irregularity or polyp merits proctoscopic examination. The forefinger has remained in the vagina during this part of the examination. With these two fingers, the cul-de-sac and uterosacral ligaments are carefully explored. This combined recto-vaginal examination is quite helpful in the determination of endometriosis, inflammatory disease, and malignant lesions of the cul-de-sac, which may not be palpable by vaginal examination alone.

In the standing position with legs somewhat apart, the fingers again are placed in the vagina to test, on bearing down and straining, the presence of cystocele, rectocele and descensus of the uterus. A much better evaluation may be obtained by examination in this position, since this is the position in which the symptoms of the disability occur.

Next, the *back* is carefully inspected, if there are symptoms of backache, and this is a prominent complaint in women. The position of the spine, its normal and abnormal curvatures (kyphosis, lordosis and scoliosis), rigidity, areas of tenderness, particularly over the lumbosacral and sacroiliac joints, are most important in the evaluation of backache, because almost all severe and acute back pains are not caused by gynecologic disease. If pain is more marked in these areas on motion backward and forward, and stretching from side to side, then the origin of symptoms must be related to disease in this area. The majority of backaches are related to difficulties along the spine itself, which includes strain, poor posture, arthritis, nervous tension, causing spasm of back muscles, or herniated discs pressing on nerve trunks.

IMPRESSION

The next point in the record is the *Impression,* which summarizes in individual diagnoses the findings of the history and physical examination. The important factors only are listed, including those from the general examination as well. This impression will affect the future consideration of this case for quite some time, which means that accuracy and thoughtful judgement are important.

DISPOSITION

The final point in the record is the disposition, which includes the various diagnostic aids that are suggested, the treatments to be given, the consideration of surgery, if indicated, and its degree of urgency, and finally the plan of follow-up of the patient.

The patient appreciates, and expects to learn the essential details of her examination, diagnosis, and projected treatments. Her many questions must be answered, and she must realize that she has a responsibility in the choice and accomplishment of treatment in her case. This is a far cry from the surgeon of yesteryear, who told his patient essentially nothing of the diagnosis, therapy, and surgery, because it was not good for her, and because she would not understand. Explanations are best presented in a calm and relaxed manner. Sometimes a complicated problem may be most difficult to present. The physician, who can explain to his patient the meaning of endometriosis, its cause, course and reasons for treatment or no treatment, in a short period of time, has successfully met, and not without much effort, this modern approach to the practice of medicine.

Frequently, when the complaints are minor, and the examination essentially negative, it is in this explanatory session that the patient must be given opportunity to present her fears and worries, which she hesitated to volunteer originally. This includes fear of cancer, husband difficulties, financial woes, sexual misunderstandings, and a thousand other ordinary and strange situations. If the physician can meet the physical and functional and emotional problems of his patient, his complete purpose will have been achieved.

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CHAPTER II

Hormones in Gynecology

HYPOTHALAMUS

In the consideration of hormones in gynecology, one must begin with a discussion of the hypothalamus and its regulatory effects. The hypothalamus, a nerve center in the mid-brain, specifically regulates rhythmic functions in the body. This regulatory function is in large part automatic, or contained within itself in its origin, but also it is affected by the higher cortical centers, involving thought and emotion. Abnormalities in general physical health, emotional upheavals, and "run-away" glandular function probably seem to reflect back on the hypothalamus and interfere with its normal rhythmic function.

At any rate, the hypothalamus does regulate certain rhythmic functions, such as the diurnal temperature variation, in which the body temperature is one or two degrees higher in the evening than in the early morning. Apparently this is not related entirely to rest and the basal condition of the body on the one hand, and exertion and increased metabolism on the other, but there is evidently a true rhythmicity. The rhythmn of menstrual function also is determined by the hypothalamus. The stimulatory effects on the pituitary gland are indirectly responsible for the development of the endometrium in its cycle, and for the regularity or irregularity of menstruation. There are probably many other rhythmic regulatory functions that are similarly affected by the hypothalamus.

Apparently the stimulation extends through a nerve pathway into the posterior lobe, the neurogenic portion of the pituitary gland, where either an unknown hormone secretion of the lobe itself is formed and seeps through into the anterior lobe to cause its cyclic effects, or perhaps a nerve interchange system carries the stimulus from the posterior lobe over into the anterior lobe. The exact nature of this intermediate mechanism is not clear.

While various systemic diseases may directly affect the hypothalamus and its function, of particular interest is the relation of emotion. Actually, it seems that the hypothalamus in some instances must be the seat of origin of emotional changes in humans, as indicated by tumors and other lesions that develop in this area, but also the hypothalamus is affected by those emotions that may arise in the cortical centers, in which a nerve effect seems to extend from the cortical center to the hypothalamus and interfere with its regulatory action. Anxiety and tension, with its cortical stimulation, may affect the hypothalamus to cause abnormal and irregular stimulation of follicle stimulating hormone (FSH), without the subsequent secretion of luteinizing hormone (LH) and luteotrophic hormone (LT H), so that excessive estrogenic stimulation may be produced by the ovary in an irregular manner, to cause irregular and prolonged menstruation. Again, the ovulatory type of bleeding, associated with corpus luteum formation without its complete involution at the proper time of the cycle, may produce menorrhagia. An incomplete stimulation from the hypothalamus may produce a hypogonadal stimulus, so that amenorrhea results. This is known as hypothalamic amenorrhea. Many have felt that the majority of cases with secondary amenorrhea fit into this group, and that the cause is related to emotional tension. The mechanism of sterility in patients with anxiety and tensions, many of which are unrecognized, is unknown, and yet the psyche seems to be a very definite factor. Probably the psychogenic factor in sterility is mediated through the hypothalamus. These, and undoubtedly many other functional conditions are related to irregular action of the hypothalamus, and investigation in this area is continuing.

PITUITARY GLAND

The pituitary gland, the master gland of internal secretions, affecting all of the other glands by directing them in their effects, controls ovarian function directly by three hormones: follicle-stimulating hormone, luteinizing hormone, and luteotrophic hormone, each known as FSH, LH, and LTH. The three types of cells in the pituitary gland, the eosinophile cell, the basophile cell, and the chromophobe cell, are known to have certain hormone secretory effects. The eosinophile cell particularly secretes the growth hormone, and abnormal secretion may be responsible for gigantism, acromegaly, or dwarfism. The basophile cell is thought to secrete the gonadotrophic hormones affecting the ovaries and testicles. The thyrotrophic, adrenotrophic, and lactogenic hormones also probably arise from the basophile cell. The chromophobe cell may be a replacement cell, but also may have other, poorly understood, functions. The remarkable change in the chromophobe cell during pregnancy, in which it becomes greatly enlarged and prominent, is a response, the importance of which is unknown. The pregnancy change in the chromophobe cell may be caused by chorionic gonadotrophin, since it occurs in association with both pregnancy and with hydatidform mole and chorionepithelioma, also occurring with the latter when there is an extragenital chorionepithelioma entirely unrelated to a pregnancy in itself. It remains possible that the change in the chromophobe cell may cause the development of the malignant tumor, in contrast to an opposite and incidental effect. The "castration cell" has been noted in the pituitary gland; it represents the enlarged and vacuolated basophile cell appearing after excision of the gonads, or in many instances after the menopause. Evidently, it either represents a functional secretory change after removal of the gonadal hormones, or it is a simple effect of the absence of these hormones.

In 1928, Zondek and Aschheim performed epoch-making experiments; they found in the urine and serum of pregnant women a gonadotrophic hormone, a hormone which stimulated the ovaries and testicles of experimental animals, particularly those of mice and rats. This hormone had two factors which they called prolan A and prolan B, the former stimulating the follicles of the ovary or the tubules of the testis, and the latter causing ovulation and stimulating the corpus luteum in the female, and the interstitial cells of the testis in the male. For several years it was thought that prolan, which appeared in greatly increased amount during pregnancy, represented the original pituitary hormone. Further experiments showed that when the pituitary gland was excised in the experimental animal the injection of this supposed pituitary gonadotropin had no effect on the ovaries or testicles of that animal, the effect occurring only if the pituitary gland was intact. Thus, it became evident that this hormone had its effect indirectly through the pituitary gland, evidently stimulating the pituitary gland itself. Finally, it was determined that the prolan A and prolan B arose from the placenta of the woman, and furthermore that it was secreted by the Langhans' cells. Now it is known as chorionic gonadotrophin. Its stimulatory effect is indirect through the pituitary gland. In spite of the disappointment of learning that this was not the true pituitary hormone, since the gonadotrophic effects were so obvious and marked in the experimental animal, it was thought that concentrations of this hormone would be useful in stimulating the gonads of women and men when necessary. The literature abounds with papers attesting to the excellent results of treatment with this hormone, but at the present time it is doubtful that chorionic gonadotrophin from human pregnancy urine or serum is of any material value in the treatment of any abnormal conditions in the human. Finally, there remained a single therapeutic purpose for this hormone: that it might aid the descent of undescended testicles at the time of puberty. Now it appears that even this effect in adolescent boys is a questionable one. The most recent suggestion has been that the hormone will aid in the reduction of weight when accompanied by a strict low-calorie diet. This is a far cry for the use of a hormone with a dramatic background, at one time thought to be the key to gonadal functional abnormalities in humans. Brown and Bradbury showed that extraordinarily large doses of human chorionic gonadotrophin, 5000-10000 units daily, will stimulate the human corpus luteum after it is already formed to greater and prolonged action, and that it may prevent involution of the corpus luteum at its normal time and thus delay menstruation. The clinical application of this dosage has not been evaluated in the treatment of patients.

Another chorionic gonadotrophin, at one time of exciting interest, is equine gonadotrophin. This hormone, secreted by the placenta of the mare, apparently has a much larger molecular structure, is not excreted in the urine, and accumulates in the blood serum of the pregnant mare in great concentrations. When extracted and purified, it has an extraordinary effect in the indirect stimulation of the gonads of the experimental animal. Equine gonadotrophin particularly strongly stimulates the Graaffian follicles, in contrast to the human chorionic gonadotrophin which has a predominately luteinizing effect. In 1937, exciting news by Davis and Koff (which overflowed from the medical journals into the daily press) indicated that ovulation in the human female may be produced by equine gonadotrophin. A large volume of enthusiastic literature appeared on the use of this hormone. Subsequently it has become doubtful that ovulation may be produced by this method. Certainly it seems unlikely to be produced in a majority of patients. On the other hand, there are definite stimulatory effects, the ovary becoming larger and cystic from the formation of multiple Graafian follicle cysts, such enlargement being readily palpable in patients treated with this hormone. Biopsies of the endometrium have indicated cyclic changes with secretory function in patients treated over several months. The nihilistic attitude which developed after so many failures and repudiations of published papers has relegated this hormone to an essentially useless position at this time. It should be studied in much greater detail and be re-evaluated scientifically. That it is a potent hormone and that it must affect the human ovary and testicle are reasonably documented, although the indications for its use are not clear.

The true gonadotrophic hormones secreted by the anterior lobe of the pituitary gland are now considered to be the follicle stimulating hormone, the luteinizing hormone, and the luteotrophic hormone.

The follicle stimulating hormone (FSH) appears in increasing amount near the end of the menstrual cycle, and stimulates the growth and function of the new primary follicle, the one chosen in an unknown manner to be the dominant follicle in that cycle. The FSH continues to be secreted in increasing amounts until just before ovulation, after which it dips sharply. The level rises again to a slightly lessened elevation immediately before menstruation, when it drops again to a relatively low level. Apparently, it never disappears completely during menstrual life. Since the hypothesis exists that the FSH quantitatively determines the secretion and effects of the graafian follicles, it is thought that increased amounts of the FSH may cause multiple follicular cysts, with hyperfunction and subsequent endometrial hyperplasia, associated with irregular and prolonged uterine bleeding. Actual determinations of the amount of FSH in the urine and serum of patients with endometrial hyperplasia disappointingly may show normal or varying results. With secondary amenorrhea associated with hypo-ovarianism, it is taught that there probably is a hyposecretion of FSH, the ovarian stimulus not being properly developed at the pituitary source. Again, actual determination of FSH is quite variable from one case to the other, some showing hyposecretion, the majority a normal secretion, and some an increased secretion. It is better established, and rather well documented, that excessive secretion of FSH does occur with ovarian dysgenesis, or Turner's syndrome, in which the primary difficulty is an incomplete development or almost total undevelopment of the gonad; this is discussed further in the chapter on intersex. The pituitary stimulus is present and overdeveloped in these cases, probably because there is no depressing and counterbalancing effect from gonadal hormone. Likely all cases of primary amenorrhea, or the vast majority, fit in this group of gonadal agenesis, or gonadal dysgenesis, but perhaps some are of pituitary origin itself with a hyposecretion of FSH, so that the relatively immature but normal gonad is simply not stimulated to rhythmic function.

After the menopause, whether produced by normal atrophy of the ovary or castration, as indicated in its completion by the absence of estrogenic effects, the secretion and excretion of FSH increases greatly in amount. The so-called menopausal hormone is the true FSH, is secreted by the anterior lobe of the pituitary gland in increased amounts, perhaps has a function in the production of menopausal symptoms, although this is only theoretical, and probably appears in large amount because the counter effects on the pituitary gland from estrogen and progesterone are totally removed. This menopausal hormone has been extracted from the urine of women after castration and after a normal menopause, has been concentrated, and has been used to produce some degree of follicle stimulation in the woman, but not for a practical purpose at the moment (Brown *et al.*).

The luteinizing hormone, LH, is secreted in sudden amount on about the twelfth or thirteenth day of the menstrual cycle, and is thought to be responsible for the discharge of the ovum, or ovulation. This hormone continues to be secreted and causes the formation of the corpus luteum, the change of the granulosal cells into luteinizing cells in which they become greatly enlarged and contain a large amount of lipoid material. This luteinizing hormone which apparently causes ovulation and the structural form of the corpus luteum, but not the secretion of progesterone, has been extracted experimentally in small amount but has not been used in the human female.

The luteotrophic hormone, LTH, is thought to be secreted by the anterior lobe of the pituitary gland immediately after ovulation in continuing and perhaps increasing amount up to three days before menstruation. This hormone is thought to be responsible for the activation of the corpus luteum to secrete its progesterone. Experimental studies have indicated that LTH may be identical with the lactogenic hormone, the hormone that triggers the secretion of milk in the breasts after delivery. On the other hand, the LTH may be quite separate and have only some similar qualities, as these hormones have not been completely isolated and separated, nor have their clinical structures been determined.

Apparently the LTH is not formed at all in anovulatory cycles, and is not present with endometrial hyperplasia with its subsequent irregular menstruation and prolonged metrorrhagia. Apparently it is secreted in abnormal amount, seemingly increased, with the prolonged functional corpus luteum which may produce menorrhagia, or the corpus luteum cyst, which may persist and cause delayed menstruation for a few days or a few weeks. On the other hand, theoretically it seems that the LTH may be diminished with incomplete ripening of the endometrium, with the so-called mixed endometrial patterns in which a portion of the endometrium shows secretory effects and the remainder no secretion. These mixed patterns are associated with metrorrhagia and menorrhagia, though much less frequently than is the pure non-secretory or well-formed secretory endometrium. Abnormal endometrial findings, when associated with absent, diminished or decreased secretory effects, apparently are related indirectly to the amounts of LH and LTH secreted by the pituitary gland. Lactogenic hormone has been used for experimental clinical studies by Holmstrom and others. This may represent the LTH. Its usefulness has not been clarified.

THE OVARY

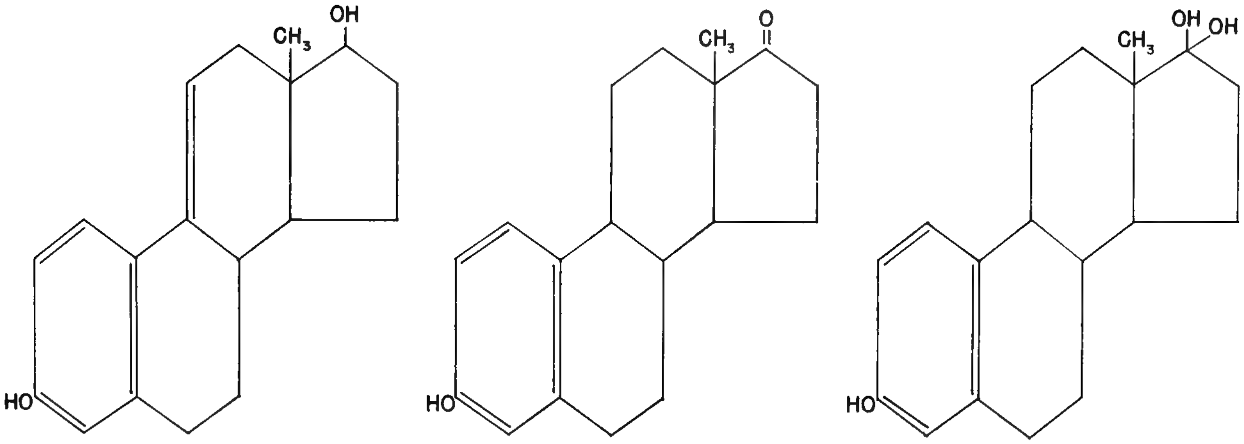
The ovary, the testicle, and the adrenal cortex secrete steroid hormones, hormones that have a close chemical relationship, that are rather similar to the formula of cholesterol, which may be the basic origin of the steroids. Figure 4 shows the chemical formulas of these various hormones and their relationship.

Estrogenic Hormone

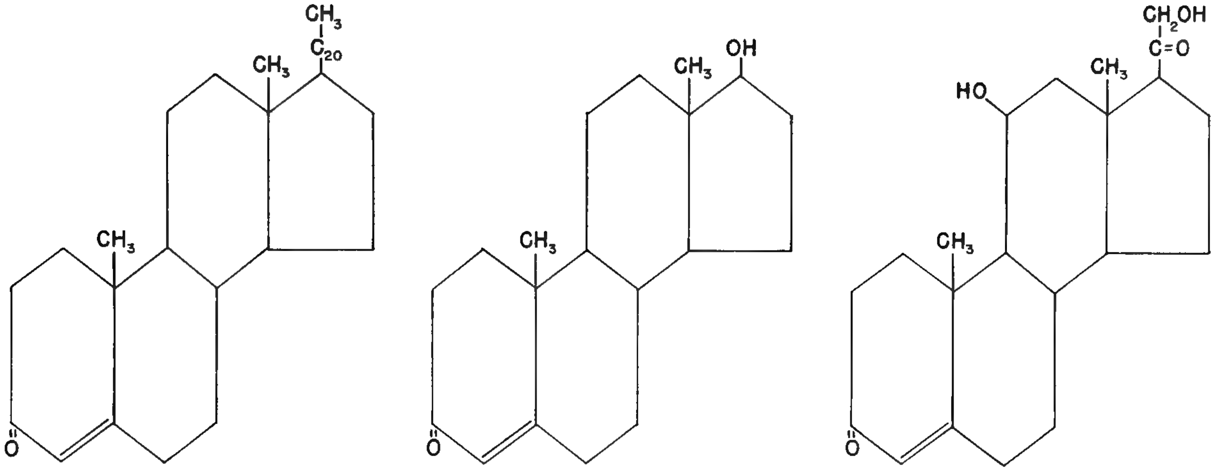
Estrogenic hormone is produced by the granulosal cells of the graafian follicles as estradiol. This primary ovarian hormone is secreted into the liquor folliculi, and is absorbed into the blood stream and circulated over the entire body. It is produced in gradually increasing amount as the cycle progresses, beginning near the end of menstruation and rising to a high level immediately before ovulation, when it dips sharply with the rupture of the graafian follicle. Then it slowly recovers to almost the same level in the blood stream, or perhaps a higher elevation immediately before menstruation, when it drops sharply to a definitely low level. This drop is a factor in bleeding from the endometrium. Thus, it is evident that not only the granulosal cells secrete estrogenic hormone in the first half of the cycle, but that the same cells when transposed to lutein cells continue to secrete estrogen generously up to the time of menstruation.

Estradiol, absorbed into the blood stream after secretion by the granulosal cells of the primary follicle, the dominant follicle of that cycle, also is produced by many of the supporting follicles which develop and function in that menstrual cycle. The circulating estradiol is partially metabolized by the liver to form estrone and estriol, after which all three estrogens, and there are others formed in metabolism that have been isolated, circulate together over the body and have both their local and generalized estrogenic effects. The excess passes through the glomeruli of the kidneys, and is excreted in the urine. The proportions of the three known estrogenic hormones may be determined by complicated chemical and biological analysis.

The estrogenic hormone is primarily a growth hormone, as related to the genital tissues. The entire genital tract is largely dependent on the presence of estrogen for its growth and development. The fallopian tube, in its gross size, diameter, length, and the villous formation in the interior, and particularly the tubal epithelium involving the secretory cells, the ciliated cells, and the peg cells, are greatly dependant upon estrogenic hormone. From the increasing amount of estrogen after menstruation up to



ESTRADIOL ESTRONE ESTRIOL



PROGESTERONE TESTOSTERONE CORTICOSTERONE

Fig. 4. Steroid hormones of interest in gynecology. The best known estrogens found in the human female include estradiol, the primary estrogen produced by the ovarian follicles, and estrone and estriol, which are metabolites of estradiol. Actually, twelve other estrogens have been isolated from women. Progesterone, testosterone and corticosterone have striking similarities in their formulas.

the time of ovulation, a marked effect occurs in the elongation and apparent function of these tubal epithelial cells.

The endometrium shows the most sensitive effect from estrogenic hormone, as a growth acceleration of the stromal and the epithelial cells lining the glands. The latter proliferate under the stimulation of estrogen and produce the covering of the endometrium when denuded. If a normal or less than normal amount of estrogen is produced throughout the cycle, even though ovulation and corpus luteum formation does not occur, the endometrium develops to approximately normal thickness. When the estrogen is withdrawn, there follows withdrawal bleeding from this estrogenic endometrium. This is called "anovulatory menstruation," a sterile situation which is relatively infrequent in the regularly menstruating woman, probably occurring only once or twice in each twelve months. If there is excessive secretion of estrogenic hormone over a prolonged period of time, or if there is a continuous secretion of a normal amount of estrogenic hormone without appreciable interruption over a prolonged period of time, both unopposed by any luteal effect (progesterone), then the endometrium may become increasingly thickened to an abnormal degree, with the formation of dilated non-secretory glands, a "swiss cheese" pattern of endometrial hyperplasia. Such a change in the endometrium with the dilated cystic glands may recede into a normal appearing non-secretory endometrium, only to reform the dilated glands at varying short intervals of a few weeks. Apparently this is related to the amount of estrogenic hormone present. This hormone effect, produced by continuous or excessive and unopposed secretion, causes an important and relatively frequent functional abnormality in women.

The development of the myometrium, including the formation of its blood vessels, is definitely related in part to the amount of estrogenic hormone present. The growth hormone here is not so obvious and sensitive as in the endometrium. Progesterone has some definite effect on the growth and development of the uterus, and in some direct or indirect manner it appears that thyroid hormone has some relationship. The cervix of the uterus similarly is in part related in its growth to the estrogens present; in fact, the estrogens are quite important. However, there are other congenital and hormone effects as mentioned in further discussion of the myometrium that definitely affect the growth and development of the cervix. This applies not only to the connective tissue and muscle in the body of the cervix but also the endocervical glands. The cervical mucous secretion is largely produced by the estrogenic hormone present. The normal variation of estrogenic hormone causes an increased secretion of mucous near the time of ovulation and in the few days preceding menstruation. Excessive estrogen may cause a marked secretion. Other causes of profuse or increased secretions are infections, congestion related to vasomotor changes, and neoplasm under rare circumstances. For the most part, the production of the cervical mucous is particularly related to the estrogens. A normal cervical mucous is quite important in fertility. The cervical mucus when dried produces arborization or fern formation due to a crystallization of sodium chloride in the mucus, when there is unopposed estrogenic effect. A markedly diminished estrogen will give none of this arborization phenomenon due to absence of appreciable sodium chloride. Excess unopposed estrogen causes marked arborization. When progesterone appears after ovulation, the secretion of the sodium chloride is halted and the arborization phenomenon, or fern-like crystallization, disappears. This mechanism may be used in the daily study of patients, as it gives some added information regarding the hormonal status at the particular time.

The vagina is most sensitive to the estrogenic hormone, and perhaps is more sensitive than the endometrium, although both are quite responsive to this genital growth hormone. These growth effects are most obvious when the mucous membrane of the prepubertal vagina becomes extraordinarily thickened due to the hormone stimulation when puberty appears. Subsequently the opposite change of the estrogenic vagina into the postmenopausal atrophic vagina, with its relatively few layers composed of the immature cells, is a great contrast to the quite mature cornified cells of the estrogenic vagina. These changes are readily distinguished by studies of vaginal smears, stained by various methods, or by studies of vaginal washings suspended in normal saline solution. Less obvious changes occur within the normal menstrual cycle. One particular change in the cells occurs immediately after menstruation, when the level of estrogens is at its lowest in the cycle. Then the majority of cells shed are of oval and round appearance, immature cells from the thinner lining.

The growth and development of the vulva also is related to the amount of estrogen present. Degrees of hypodevelopment of the vulva are seen frequently with genital hypoplasia and apparent hypoestrinism, although in part this may be related to other congenital factors that prevent development of the genital tissues. The presence and growth of the hair of the vulva is related to estrogenic hormone, but this is not the only factor. A certain amount of hair may develop with gonadal agenesis or dysgenesis, and apparent complete absence of estrogenic hormone. Excessive estrogen, and this is noted especially when given therapeutically in excess, may produce marked congestion, edema, and enlargement of the vulva with associated discomfort. Lesser degrees of congestion may be related to a temporary or chronic state of sexual excitement, affected by local vasomotor changes and perhaps by emotional stimulation of the hypothalamus with final increased estrogenic effect.

The skin of the entire body and the other mucous membranes, particularly that of the nose and mouth, are quite affected by estrogenic hormone, especially in growth of the epithelium. The skin of the body is perhaps less sensitive, but is a secondary sex organ, the thickness being definitely related to estrogen. This is most obvious in the observation of the elderly woman with very thin, rather transparent skin. This is in contrast to the woman with ovarian function where the skin is thick, resilient, and opaque. The clinical signs of aging of the skin include pallor, yellowness, wrinkles, dryness, loss of elasticity, diminished oil and deterioration of texture. The skin becomes thinner, and cells of the basal layer and prickle cell layer become vacuolated. The papillae flatten. The elastic fibers show clumping, shortening, and thickening. The sebaceous glands are reduced in number. (Traub and Spoor, 1953).

Partial reversal of the changes in the skin of the elderly woman has been produced experimentally by the local application or the systemic administration of estrogens (Sulzberger *et al.*). The use of estrogenic creams as cosmetic preparations does have merit in strictly atrophic conditions that may develop after the menopause. Atrophy of the various mucosal linings, which occur after the menopause or in the absence of estrogen, may be aided by systemic estrogen or local estrogen. The treatment of atrophic rhinitis by estrogenic therapy in the woman with normal estrogens is of questionable value.

The breasts are sensitive to estrogenic hormone, at least in degree, and sometimes may be developed markedly by estrogenic therapy. The ducts of the glands of the breast especially are stimulated by estrogen, proliferating and retracting during the menstrual cycle. An obvious contrast occurs in the woman with normal estrogens and the prepubescent child or the postmenopausal woman. However, the growth of the breast is not related to estrogen alone, because in some instances excessive administration causes little change in the breast. There must be some other factors, either congenital ones or other hormonal factors that are not understood, which are necessary in the development of the breast. Local estrogenic creams have been used, being applied daily to the breasts, and have shown some degree of breast enlargement but this appears temporary and not of practical value.

Progesterone

The corpus luteum hormone, progesterone, is secreted from the lutein cells. The cells that originally were the granulosal cells, those that produced estrogen alone, now produce progesterone, but also an increasing amount of estrogen (estradiol). The progesterone primarily has a secretory effect on the endometrium. This is described in detail in the chapter on the endometrium. In addition, the myometrium is affected considerably by progesterone, which causes edema, enlargement of the muscle fibers, and increased blood flow through the myometrium. Probably there must be some increasing amounts of estrogen present to produce the enhanced effect of the progesterone.

Progesterone neutralizes the temperature-depressing effect of estrogen, and allows the temperature, lowered by unopposed estrogen, to rise approximately one degree, the normal for that individual. Its understanding is important in the interpretation and study of thermal charts. Some think that an incomplete rise in the temperature indicates a proportionate deficiency of progesterone.

The secretory effects of progesterone on the endometrium appear earliest as the basal globules in the late interval or early ovulatory endometrium. Later, sawtoothed glands with ragged cells develop and glycogen globules are discharged into the lumen of the glands. In early pregnancy the increasing progesterone produces great swelling of the stromal cells, which are filled with glycogen and which produce enlargement of the zona compacta and form a soft "feather bed" for the young embryo. For decidua to form as shown experimentally, pure progesterone must be available in from thirty-five to fifty mg. per day (in oil), and for decidua to remain intact there must be present an amount of estrogen equivalent to one mgm. of stilbestrol daily (Bradbury *et al.*). For the decidua to remain intact longer than two months, progesterone and estrogen must be present in increasing amounts; otherwise, necrosis and sloughing of the decidua will occur.

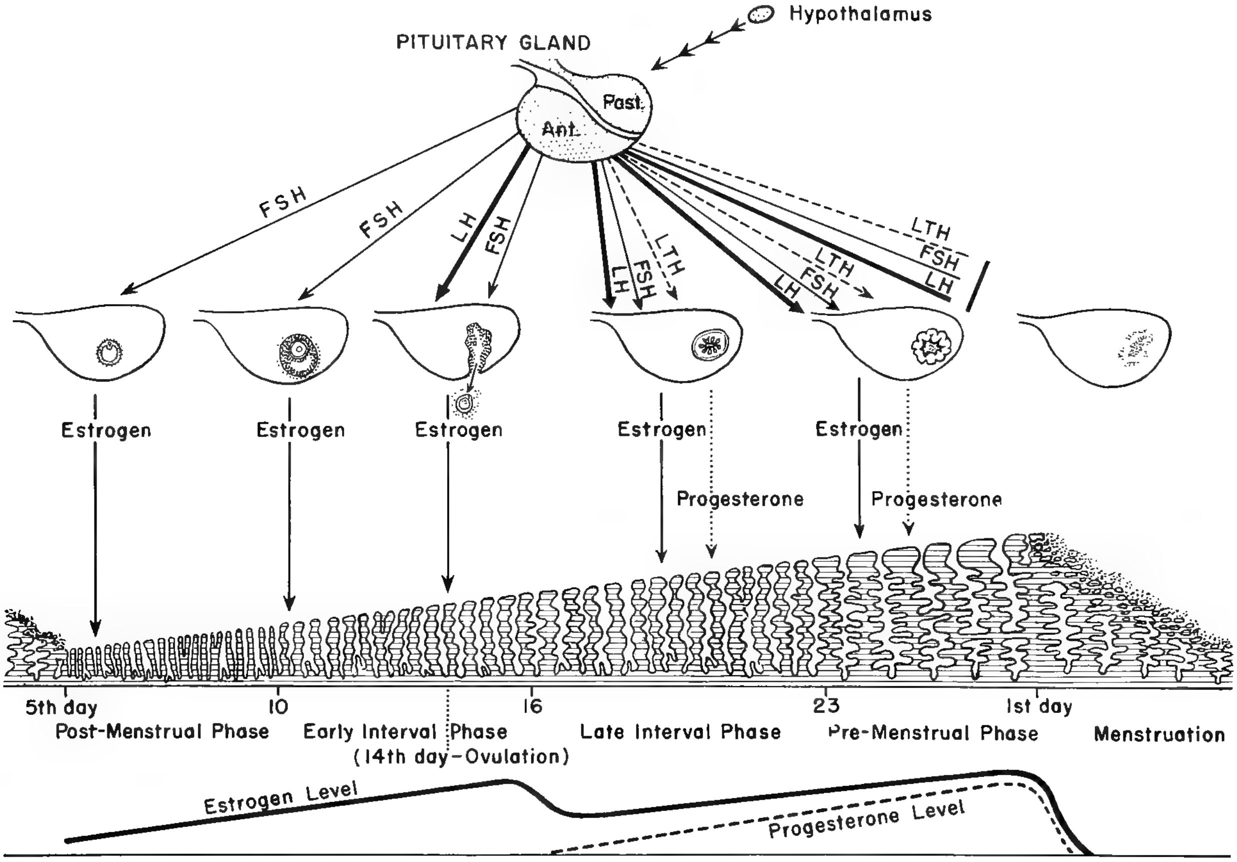


Fig. 5. Hormones of the menstrual cycle. The hypothalamus stimulates the anterior lobe of the pituitary gland by way of the posterior lobe. The follicle stimulating hormone (F. S. H.) is produced throughout the cycle in varying amounts. Luteinizing hormone precipitates ovulation. Luteotrophic hormone is necessary for function of the corpus luteum. Estrogen causes growth of the endometrium. At first the glands are straight (post-menstrual), then slightly curved (early interval). After progesterone appears from the corpus luteum, the glands become more curved and show early secretion (late interval phase). Finally, the glands become saw-toothed and discharge their glycogen into the lumen (premenstrual phase). The removal of progesterone and estrogen causes spasm of the spiral arterioles and fragmentation necrosis occurs (menstruation). The estrogen level dips at ovulation and drops precipitiously before menstruation. The progesterone level also drops sharply before menstruation.

Progesterone has an important effect on the breasts. The estrogen causes proliferation of the ducts, whereas progesterone causes enlargement of the acini. Progesterone plays an important part in the formation of chronic cystic mastitis, in the increased fibrosis, the so-called fibrocystic disease of the breast, which appears primarily in the premenstrual phase and regresses in degree in the postmenstrual estrogenic phase. Chronic cystic mastitis, or fibrocystic disease, or fibroadenomatosis of the breast, disappears after the menopause, and as a rule is not reformed by estrogens alone, although tenderness of the breasts, swelling, pain, and occasional cysts may develop from estrogen alone.

Normal premenstrual tension evidently is caused by the presence of progesterone. In the last two weeks of the menstrual cycle, there is increased tension in every woman. If the ovaries are in an anovulatory phase, the tension does not develop. When the tension becomes pathological, it appears that there are other reasons for anxiety that exacerbate the normal premenstrual tension. Associated with this period is water retention, caused by the retention of sodium in the tissue space in the body. Similar water retention is thought to occur in the brain, and perhaps this may be responsible for some of the premenstrual nervousness. In occasional women, the water retention may be most severe with gains in weight of ten to fifteen pounds in the few days before menstruation, to be followed by diuresis and weight loss following menstruation.

Acne of the face, chest and back, particularly in young women, is related to progesterone. Perhaps this is an androgenic effect of progesterone, a hormone more closely related to testosterone than the estrogens; it is known that progesterone does have some androgenic effect.

Progesterone is necessary for the maintenance of normal pregnancies. It is produced first by the corpus luteum, but as the placenta is formed the production largely is taken over by this organ of the fetus, being secreted by the Langhans' cells.

ESTROGENS FOR CLINICAL USE

The first estrogen isolated by Doisy, Thayer, and Veler, in 1929, was called theelin, now known as estrone, and was thought to represent the original estrogenic hormone from the graafian follicles. Later (1936) it was considered that the original hormone is estradiol and that estrone is a metabolic product. At any rate, estrone has been used widely in the treatment of various conditions in which estrogens are indicated, and it is quite satisfactory as an injectible estrogen and has a fair oral potency. There is evidently no difference whatever in the various estrogens in the subjective effect on the patient, certainly not of the natural estrogens, and estrone and estriol may be just as effective as estradiol if given in sufficient dosage. Many different brand names of estrone have appeared over the past thirty years. Estradiol has been used in the free form as an oral tablet and as a pellet for implantation and prolonged absorption. More frequently and more commonly it has been used in an injectible form, as estradiol benzoate, or other comparable or related esters. This injectible estrogen has a physiologic effect of from one to three or four weeks, and is quite potent. The dosage is about one-fifth or one-tenth that required of estrone to derive the same effect. However, the fact that a smaller amount is required to give the same effect does not mean that the drug is necessarily better. Ethinyl estradiol is an extraordinarily potent estrogen, far more potent than the other estradiol esters, especially when given orally in the smallest amount. In 1942, there appeared a mixture of conjugated estrogens, containing principally estrone sulfate and equilin, being prepared from the pregnant mare's urine. This product, known principally as estrone sulfate (Premarin), has an excellent estrogenic effect when given orally. Bradbury has indicated that the equilin in this product is more important and more potent than the estrone sulfate, which has been stressed as the principal ingredient. At any rate, the combination is quite satisfactory in the treatment of patients. In 1935, stilbestrol was introduced as a synthetic estrogen, and many clinical reports began to appear in 1939 and 1940. It has an extraordinary effect when used orally, being more potent than the natural hormones. It is not a hormone, having an unrelated chemical formula, characterized by two benzene rings in a chain. This estrogenic substance does have certain disadvantages, mainly that of nausea which occurs in from fifteen to thirty per cent of patients who are receiving this drug. A much smaller percentage may develop a rash of the skin. Quite rarely diarrhea may occur. However, this estrogen is widely used because of its great economy and marked potency. Many derivatives of stilbestrol have been prepared and are satisfactory estrogens.

The clinical uses of estrogens are numerous, but the most important is the treatment of the menopause. This is elaborated upon in a separate chapter, because of its importance and varied nature. A second important use of estrogen is the treatment of prepubescent vaginitis on the one hand, and atrophic vaginitis after the menopause. These two conditions are quite similar. In each instance, the vagina is covered by five, six or eight layers of squamous epithelium. This is a relatively thin layer; the cells have not matured into the stratified squamous hexagonal cornified epithelium. They are shed into the vagina largely as the oval and round cells of the parabasal type. These thin, undeveloped or atrophied vaginas have a pH of six, seven or eight, and are readily inflamed by varying bacteria, many of which must come from the anal orifice, especially in the prepubescent child. One difference among others is the susceptibility of the prepubescent anestrogenic vagina to gonorrheal infection, whereas this infection rarely occurs in the postmenopausal vagina. The cure in each instance may be achieved by administration of various estrogens, whether given orally, parentally, by vaginal suppositories, or in a vaginal cream. In the prepubescent child, the estrogenic cream (Premarin vaginal cream, dienestrol cream, etc.) is applied to the vulva and vestibule each night for two or three weeks, and then twice weekly for two or three months. These applications cause the vagina to become quite thick, to develop an acid secretion of pH 4.0, and to have an entirely different flora in the vagina, consisting principally of the Doderlein bacillus, which is found in the normal adult vagina. In the postmenopausal vagina, similarly a cream may be applied to the vulva, but better results follow the introduction of the hormone cream into the vagina once or twice weekly. Relatively little hormone and a small amount of cream is necessary to give an excellent effect, as the vagina is very sensitive to the local application of estrogens. Similarly urethritis and trigonitis in postmenopausal women, with symptoms of burning on urination and frequency, may be improved by estrogenic therapy, which thickens the transitional epithelium.

Another use for estrogen is that of increasing the cervical mucus. A proper amount and character of cervical mucus is necesary in fertility. Some cervices in sterile patients produce a mucus that is inimical to the husband's spermatozoa, causing immobilization of the sperm. Apparently the use of small doses of estrogen, whether as stilbestrol or natural estrogens, may produce an increased amount of mucous, which may be more inhabitable for the virile spermatozoa. The dose of estrogen must be less than that which will interfere with ovulation.

In patients with primary amenorrhea, withdrawal bleeding may be useful for psychological purposes, especially since spontaneous menstruation is not to be ex-

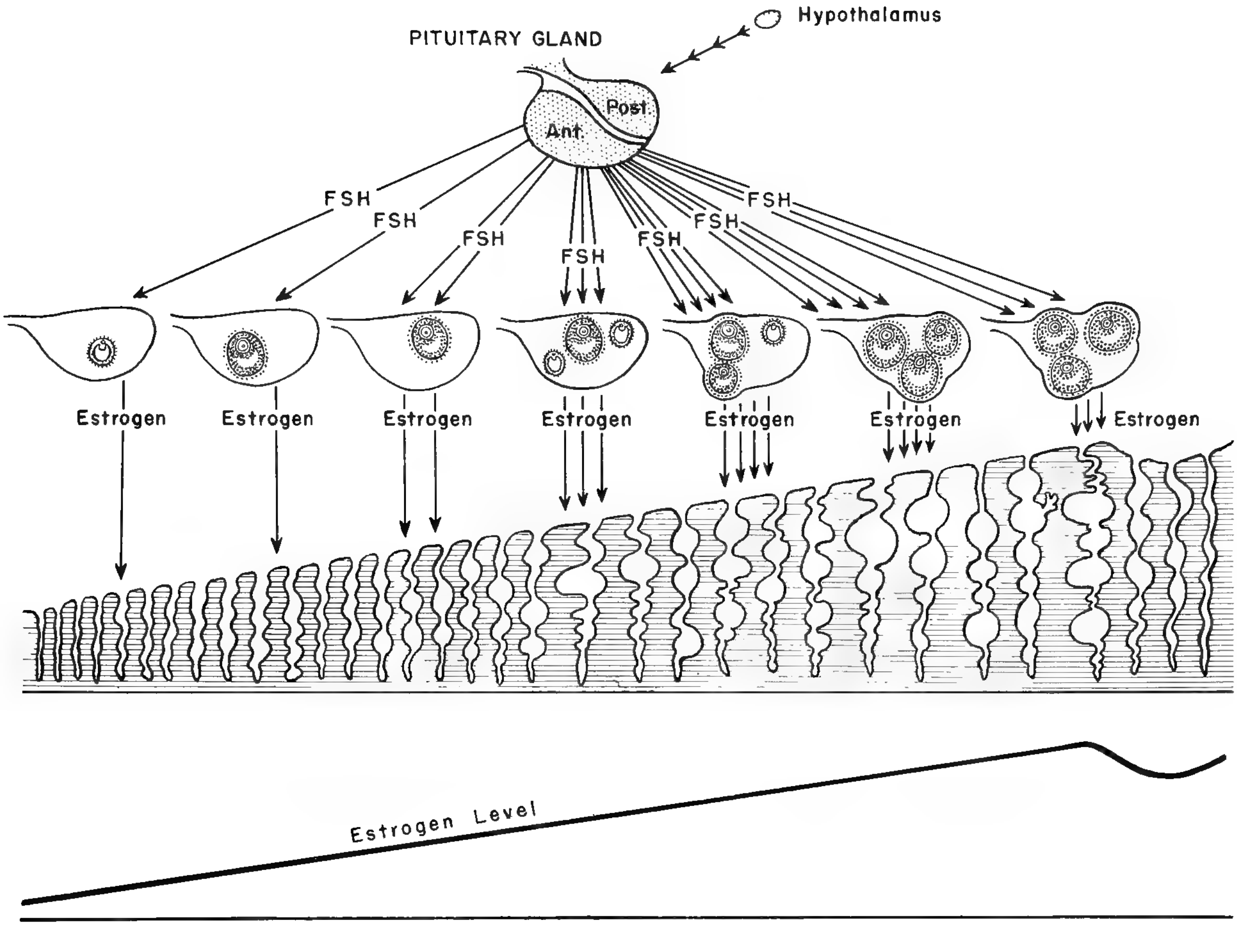


Fig. 6. Hormones in anovulatory menstruation, metrorrhagia and endometrial hyperplasia. The hypothalamus stimulates the anterior lobe of the pituitary gland through the posterior lobe. Follicle stimulating hormone stimulates the ovary excessively, in a prolonged and irregular manner. The graafian follicles may form cysts and secrete increasing amounts of estradiol. The growth effect on the endometrium shows first a post-menstrual phase, then early interval phase, and finally, endometrial hyperplasia, with its thickened endometrium and "swiss-cheese" appearance. Ovulation has not occurred, and the endometrial glands show no glycogen globules. The prolonged, sustained, and elevated estrogen level in the blood produces the endometrial hyperplasia. After varying periods of time "break-through" bleeding may occur, and with drops in the estrogen level, prolonged withdrawal bleeding may occur.

pected. With secondary amenorrhea, a few induced cycles may be followed by normal menstruation. Stilbestrol from one to five mgm. may be given daily for twenty days, or Premarin from one to five mgm. daily for twenty days. These courses of treatment may be repeated every twenty-eight days, for several cycles. Three to five days following the last dose of estrogen, bleeding occurs from the estrogenically stimulated endometrium, not as a crumbling away as with the progestationally prepared endometrium, but by ulceration and slight fragmentation.

Menometrorrhagia may be controlled by estrogens, particularly in the young patient with prolonged and irregular bleeding. In this instance, she may be given a similar amount of estrogen for twenty out of every twenty-eight days, each course of treatment being followed by withdrawal bleeding that simulates normal menstruation. Such controlled bleeding should not be used in women after the age of twenty-five years until curettage and biopsies for studies of the endometrium and cervix have been made in order to rule out malignancy. It is tragic to find the occasional case with malignancy which has been treated for months as a functional bleeding case. For recurrent bleeding after curettage, one may use estrogenic therapy, though it should be given only if necessary.

Estrogen may be used to inhibit ovulation in cases with severe dysmenorrhea. If one prescribed stilbestrol one mgm. daily for one week following the menstrual period, two mgm. daily during the second week, and three mgm. daily for the third week, painless withdrawal bleeding will occur, as anovulatory menstruation, three to five days later. Larger doses of stilbestrol or the natural hormones may be necessary to assure the interference with ovulation in subsequent months. In a similar manner, testosterone may be given immediately following menstruation, before ovulation can occur, and thus may prevent ovulation. This is a temporary and non-curative treatment to prevent functional dysmenorrhea for a few cycles in the individual with extraordinarily severe pain.

Estrogens may be used to cause increased growth of the uterus in patients with hypoplasia and symptoms of oligomenorrhea, hypomenorrhea, and dysmenorrhea. However, this growth effect is usually disappointing, the uterus being rather insensitive to the estrogen. If progesterone is added to the estrogen, the growth may be enhanced. Thyroid hormone seems to be helpful in slowly promoting the growth of the uterus.

The development of breasts by the use of estrogens has had rather poor success, except in the patient with primary amenorrhea and little or no breast development. Breasts of patients without estrogens may grow after estrogenic therapy, but in the normally menstruating woman with small breasts no improvement can be expected by further estrogenic therapy. McBride applied estrogenic ointment to the breasts and showed enlargement from their regular application. However, it appeared that such enlargement was temporary, and that little or no lasting effect followed.

The treatment of acne with estrogens is rather firmly established in the dermatologists' armamentarium, somewhat to the discomfort of the gynecologist who sees the young patient with abnormal menstrual cycles, or prolonged bleeding, caused by the use of the estrogenic hormone. Discontinuance of the hormone causes reversion to normal cycles as a rule. That estrogen may aid the acne in these young women is true, although the results are not astounding or as good as one might hope. Apparently improvement from estrogen lies in the anatagonism to androgen which appears in the blood of the adolescent patient, both male and female. Until the male skin can become accustomed to these androgens, if such is the cause, acne may be a difficult problem. Until the androgens are perhaps further neutralized by increasing estrogens, or until they diminish in their effects, acne may be a most troublesome problem to the young woman.

The suppression of lactation and postpartum breast engorgement has been attained by estrogenic or androgenic therapy given for a few days after delivery. Varying degrees of success have been reported.

The metabolic activity of estrogens is apparent in the general improvement of the elderly woman. The anabolic mineralization of bone in the treatment of osteoporosis in postmenopausal women seems well established, but estrogenic therapy may be exceeded by androgenic therapy, or a combination of both. In geriatrics these hormones seem of great value. Apparently the combination of hormones may be helpful for the elderly male with osteoporosis.

The acceleration of epiphyseal closure by administration of estrogens in excessively tall pubertal girls has been reported, and may be of value as a treatment. Efforts to halt growth of girls growing too tall by estrogens, and results, have not been well documented.

Arteriosclerosis and coronary thrombosis may be diminished in occurrence in postmenopausal women if small doses of estrogen are given. Much interest is developing in this approach.

The inhibition of metastases in advanced incurable breast carcinoma in women five years or more after the menopause may be of marked degree, with relief of pain and discomfort, regression of the tumors, and prolonged life for several months or years. Not all postmenopausal tumors are depressed by estrogens, and only a trial of therapy can determine the sensitive tumors. On the contrary, no estrogen should be given to the younger woman with carcinoma of the breast, as it appears that thirty to forty per cent are estrogen dependent, that is, are stimulated to grow and metastasize by estrogens present. It does not appear that estrogens cause breast cancer, but many are stimulated to grow more rapidly in younger women, though the opposite may occur in older women.

PROGESTERONE FOR CLINICAL USE

Progesterone has been used since 1934 as the pure hormone dissolved in sesame oil, ten to fifty mgm. per cubic centimeter. It has been administered by intramuscular injection. Ethisterone (Pranone), a derivative of progesterone, which is similar to testosterone, with a definite though very slight androgenic effect, has a useful progestational effect when taken by mouth. The dosage is about five to ten times that required by intramuscular injection of progesterone. In the past three years, long-acting progesterones, as Delalutin (Squibb), have been available for injection in oil in 125 mgm. to 250 mgm. doses, and have a prolonged effect over one to two weeks from a single injection. The injection of pure progesterone in sesame oil has an effect from two to three days, as indicated by pregnadiol excretions. Recently, Enovid (Searle) has been available on the market, containing a progestational compound of great potency (norethynodrel) combined with a small amount of ethinyl estradiol. This progestational compound and estrogen have a remarkable effect in producing progestational changes in the endometrium, causing great enlargement of the uterus, and in preventing ovulation. Norlutin (norethindrone) (Parke-Davis) is another new and exceedingly potent oral progestational compound. Other newer compounds of even greater potency are being studied in experimental use.

Perhaps the main use for progesterone has been in the treatment of threatened abortion; certainly a very large amount has been used for this purpose. The results at the moment appear discouraging, so that it is even questionable that progesterone should be used in the treatment of threatened abortion. Apparently a very rare case may need progesterone, whereas the remainder tend to form missed abortions, the progesterone preventing the extrusion of the dead embryo and useless pregnancy. Pregnandiol excretion studies performed routinely in early pregnancy may reveal the occasional one deficient in progesterone.

A more practical use for progesterone is the treatment of both metrorrhagia and amenorrhea. When progesterone is administered to an individual by intramuscular injection so that it is absorbed over a period of three to five days, and one would prefer five days for the best effect (and this may require two or three injections), the endometrium becomes sensitized anew to the progesterone if none is already present. As it is metabolized and excreted at the end of the few days' period, the removal of that sensitizing element is followed by marked vasomotor spasm in the endometrium, in turn, followed by necrosis, fragmentation, bleeding, and sloughing of the endometrium. This sloughing does not occur with endometrium having an estrogenic effect alone, as with endometrial hyperplasia or anovulatory menstruation, for in these instances only portions of the endometrium seem to come away. With prolonged and irregular bleeding from estrogenic endometrium a goodly portion of superficial endometrium may remain in situ over a long period of time. Progesterone as a treatment sensitizes the endometrium and causes it to slough down to the basalis. This method of treatment, while first mentioned by J. S. L. Brown, was really clarified and made useful by Albright (1939), and is known as the medical curettage, or Albright's curettage.

Withdrawal bleeding after progesterone is important in the treatment of functional uterine bleeding, but a thorough diagnosis must be made by curettage in all patients except pubescent and adolescent girls. With subsequent prolonged and irregular bleeding, progesterone may be used for repeated medical curettage, which produces a bleeding three days after the administration of the last progesterone. This bleeding lasts for five or six days, after which no further bleeding occurs for twenty-eight days. Progesterone may be given again to induce bleeding at a regular and predictable time. Such treatment may be repeated for several months, after which the patient is allowed to menstruate at will. Often menstruation becomes regular and normal.

Similarly, patients with secondary amenorrhea may have induced bleeding with progesterone. The hormone may be administered parenterally, orally, or intravaginally. Withdrawal bleeding follows regularly, provided there is an almost normal amount of estrogen present, at least enough to produce a thick vagina. With primary amenorrhea, in which the patient has never menstruated, associated with atrophy of the vagina and infantile uterus, bleeding does not occur after progesterone alone, but only after priming with estrogen. In such instances, estrogen is given daily for twenty days, followed by progesterone, and a satisfactory withdrawal bleeding follows.

Of late, the new and potent oral progestational compounds have been advised for the treatment of endometriosis. This is based on the premise that endometriosis is cured or alleviated by pregnancy. That endometrial nodules and implants do become greatly softened under the influence of progesterone and the estrogens of pregnancy is quite true, but that cure follows is not only debatable, but improbable. It is questionable that the present ideas of treatment with progestational substances will give a satisfactory solution to the treatment of endometriosis.

THE ADRENAL GLAND

The adrenal gland has an important effect on gynecological functional disease, and anatomical abnormalities involving secondary sexual characteristics.

While the medulla of the adrenal gland primarily secretes adrenalin, and has no direct sex hormone effects, the adrenal cortex on the other hand has remarkable hormonal actions. The cortical cells of the adrenal glands are divided into three layers, the zona granulosa, the zona fasiculata, and the zona reticularis. These cells secrete several types of hormones. On the one hand, there is secreted cortisone and related hormones which have far reaching and strange generalized effects, involving particularly the response to stress and the so-called "stress diseases," including forms of arthritis, various dermatologic diseases, undoubted connections with peptic ulcer, many or all allergic conditions, and the reactions of the individual to stress, injury, and infection.

In addition, there are androgens and estrogens secreted by the adrenal cortical cells in varying degree, which have their interrelated effects both in the obvious secondary sex characteristics and in the more general body metabolism, including the bony matrix throughout the body, protein metabolism, and to some extent the emotional outlook of the individual. The estrogens and androgens secreted by the adrenal cortex must have some balance between them, and purposes, of which many are unknown.

After castration, or after the normal menopause, frequently degrees of estrogen production continue, as indicated by the vaginal smear studies and observation of the thickness of the vagina, so that for two or three years, or until quite elderly in life, or perhaps indefinitely, a woman may continue to have produced in her body a considerable amount of estrogen. The uterus may remain of about normal size in these instances, but more often it does involute in spite of the continued estrogen secretion. While some observers have felt that the postmenopausal ovary must continue estrogen secretion over a long period of time in many instances, it seems more likely that the postmenopausal ovary has no effect in the vast majority of cases, and that estrogen secretion after a year or two from the cessation of menses must come from the adrenal gland. This seems clear again from the observations of the vagina and its desquamated cells after bilateral oophorectomy, when the incidence of prolonged estrogen effect is about the same as in the postmenopausal woman who has not had removal of the ovaries. Probably half of women have some continued estrogen secretion, or estrogenic effect, for one or two years after the menses cease, so that estrogenic therapy is not necessary at that time in these women. Some women after their menopause never have insufficient estrogen to cause menopausal symptoms. The operation of bilateral oophorectomy to remove estrogens that may influence certain malignant tumors, particularly carcinoma of the breast, may be in vain, either because the carcinoma is not estrogen-dependent or because estrogenic secretion continues from the adrenal gland Bilateral adrenalectomy as an added procedure seemed to help certain cases. Now, after oophorectomy, cortisone is used to depress the estrogen function of the adrenal gland. From thirty to forty percent of cases with carcinoma of the breast live materially longer, or have a remission after these hormone ablating procedures. Of late, hypophysectomy has proved helpful for similar purposes, removing the gonadotrophic and adrenotrophic hormones. Perhaps removal of the general growth hormone is important also.

The adrenal cortex normally secretes androgens in various forms, which are metabolized and excreted as 17 keto-steroids, the determination of which gives an accurate account of the amount of androgen present in the individual. This secretion is present throughout menstrual life, in amounts equivalent to the excretion of four to twelve mgm. of 17 keto-steroids daily. Some have postulated that a slightly increasing production of androgen from the adrenal gland in the latter years of menstrual life may be responsible for the menopause. That seems unlikely because the menopausal ovary develops a true and complete insensitivity to all hormone stimulation when this time of a woman's life has been reached. On the other hand, near the menopause frequently women note some increasing hair, particularly on the upper lip and on the body in general, which probably is caused by slightly increased androgen secretion.

Adrenal cortical hyperplasia, a marked thickening of the cortex of the adrenal glands, especially involving the zona reticularis, is associated with hypersecretion of androgen. When this hyperactivity of the adrenal cortex is of mild degree, there may be extremely little virilizing effect, noted as the slightest amount of increased hair growth, and perhaps no real enlargement of the clitoris, although the clitoris is a very sensitive indicator of the presence of androgens. This mild hypercortical change may be associated with interruption of the menstrual cycle, or loss of regularity of the menstrual cycle, or interference with ovulation. Thus, secondary amenorrhea, oligomenorrhea, and sterility related to anovulation, may be associated with mild degrees of adrenal hyperplasia. This is determined primarily by study of the excretion of the 17 keto-steroids and also the other oxy-steroids, in which a slight elevation is present. If such is true, the papatient may be treated with cortisone, which strangely depresses that portion of the adrenal cortex which produces the androgen, so that its secretion is reduced to a normal amount. She may then develop normal menstrual cycles, with ovulation, and subsequent fertility.

Moderate degrees of adrenal hyperplasia cause more obvious hirsutism, with some increased acne of the face and chest, a masculine hairline on the abdomen, slight enlargement of the clitoris, and more obvious menstrual abnormalities.

In the marked degree of adrenal hyperplasia, syndromes occur of two types. One is that occurring in the newborn child, where the hyperplasia has developed in intrauterine life. Often the masculinization may appear only as hypospadias or an enlarged clitoris, with the vagina entering into a common opening with the urethra. Such pseudohermaphroditism begins at an early stage of embryonic life, probably at three months of age. On the other hand, in the newborn child, there may be no change in the external genitalia, no excessive growth of hair, and the manifestation may be represented by electrolyte imbalance alone, with severe sodium depletion. In such instances, unless recognized, and the sodium ion is introduced into the circulation within a very short time, the patient may succumb to shock. If these immediate effects of the chemical imbalance are corrected, the adrenal hyperplasia apparently may regress and no further difficulty ensue.

The other and more commonly recognized form of adrenal hyperplasia is more obvious near the age of puberty. At first the child does not attain its normal height, so that the epiphyses are closed at about ten or twelve years of age. She develops increased hirsutism with a moderate growth of hair on the face, arms, legs, and abdomen, usually has degrees of acne of the face, chest and back, most often has marked enlargement of the clitoris to two to five cm. in length, and never develops menstruation or an estrogenic effect in the vagina. The uterus and ovaries remain extremely small; in fact, exploration and inspection of the ovaries show minute, white bands of gonadal tissue that suggests gonadal agenesis or dysgenesis. In these cases, the 17 keto-steroid excretion varies from thirty to one hundred mgm. daily. These children usually have been brought to the physician at the age of sixteen or eighteen years because of amenorrhea, marked overgrowth of hair, and shortness of stature. The identically same clinical findings may occur with the adrenal cortical adenoma, or adrenal cortical carcinoma, if of the androgen-secreting variety.

Until a very few years ago, the differential diagnosis between adrenal cortical tumors of the androgen-secreting type and adrenal cortical hyperplasia was made after perirenal air insufflation by study of the adrenal glands as shown in the x-ray film. Because of occasional air embolism, subsequently the air was injected through the perineum to the sides of the rectum into the retroperitoneal space. Later, in the erect position, the air found its way to the perirenal space. Occasional fatalities have followed this method; some have advised that carbon dioxide be used for this purpose. The time involved in the movement of the gas up around the adrenal glands allows so much absorption as to prevent the best visualization.

Patients with adrenal hyperplasia, who had previously been treated mainly by partial adrenal resection with indifferent results, now are approached by a new and better treatment, that of the administration of cortisone (Wilkins 1950). Strangely, the administration of cortisone depresses that portion of the adrenal gland that produces the androgen, so that the excretion of 17 keto-steroids may be diminished from one hundred mgm. per day down to two mgm. or three mgm. per day, a low normal range. In the treatment of a patient with these clinical findings, if the level of steroid excretion does not drop precipitously, and this may be demonstrated by intravenous cortisone over a few hours time, then one may assume that the patient has an adrenal cortical tumor, in which instance exploration of both adrenal glands is the proper procedure. One may wish the perirenal gas studies to attempt to localize the tumor, but bilateral exploration should be carried out in each instance. This may be performed by abdominal incision, or through bilateral flank incisions. The treatment of these patients with adrenal hyperplasia with cortisone is a remarkable advance, both for the patients with extreme virilism and for those with the slight changes which may cause functional disturbances and sterility.

The arrhenoblastoma of the ovary, the hilar cell tumors of the ovary, and the adrenal cortical cell tumors of the ovary, and occasional thecal cell tumors of the ovary, secrete androgens which are not affected by cortisone therapy. Careful pelvic examinations are necessary, and even exploratory laparotomy must be considered to find these cases.

THE THYROID GLAND

The thyroid gland has a strong influence on the function of the gonads. The clinical condition of myxedema with marked thyroid hypofunction, obesity, lethargy, and pudgy face, is associated with amenorrhea and is treated with small doses of thyroid extract, one-half grain or one grain daily sufficing, for the correction of this abnormality.

Hyperthyroidism, Grave's disease, or exophthalmic goitre, in its marked hypersecretion of the thyroid hormone, may or may not affect menstrual function. In one-third of the cases, the menstrual cycle is normal; in another third, there is metrorrhagia; and in the remaining third, there is amenorrhea. The cure of the hyperthyroidism, or at least its improvement, may be associated with the return of normal menstrual function.

In between these extremes of myxedema and exophthalmic goitre, there occur very many more patients with mild thyroid dysfunction. In gynecology the mild hypothyroidism is considered of great clinical importance. In these cases, the patient has varying menstrual dysfunction of either metrorrhagia or amenorrhea, oligomenorrhea with or without anovulation, and sterility with no other obvious dysfunction. She presents the clinical findings of a rather dry skin, fine hair, slight bradycardia, blood pressure at the lower limit of normal, varying from 80 to 100 mm. systolic, and with symptoms of fatigue and sometimes many other complaints as headaches, acne, constipation, and abnormal mucus secretion from the vagina.

In these instances, the basal metabolic rate may be slightly lowered, of minus fifteen to minus twenty per cent, the blood cholesterol may be slightly elevated, and the radio-active iodine uptake, or protein bound iodine, may be lowered, although the latter two tests are inconstant in mild hypothyroidism. Often one relies entirely on the clinical symptoms, and the examination and appearance of the patient. Hypoplasia of the uterus seems related to this mild hypothyroidism. The treatment of these patients includes the administration of thyroid extract daily over long periods of time, the dosage beginning at one-half grain or one grain daily, gradually being increased every two to four weeks as indicated, up to four grains or five grains daily in some instances, but more often stabilizing at one grain or two grains daily. This therapy may be followed by the return of normal and regular menstruation, of increased vitality and well being, and increased fertility.

Specialists in internal medicine tend to depreciate the gynecologists's treatment of this indefinite condition, but the majority of gynecologists continue to believe that the results are worthwhile. In all functional conditions, particularly those involving menstrual dysfunction, the thyroid factor is to be considered.

ANDROGENS IN GYNECOLOGY

Every female has an appreciable amount of androgenic hormone in her circulating blood, especially during menstrual life, and in somewhat increasing amount after the menopause. The balance of this androgen and estrogen is evidently important for the general body health; particularly it is important in the calcification of the bone, in protein metabolism, and probably other purposes unknown. The source of the androgen would seem to be mainly from the adrenal cortex, from the zona reticularis, but there are some indications that the theca ovari, the thecal cells surrounding the graafian follicles, may secrete some androgenic hormone. Not only do androgens occur normally in the female, but estrogens occur normally in the male in degree, so that the two hormones are bilateral in either the male or the female, though with opposite emphasis in each case.

For menometrorrhagia, androgen, as testosterone propionate for intramuscular injection, or free testosterone and methyl testosterone for oral administration, may be used to diminish the emphasized estrogen effect and to diminish the blood loss and continuation of bleeding. The use of as much as three hundred mgm. of testosterone propionate by intramuscular administration per month, has long been known to produce hirsutism, or degrees of virilism. More recently it is noted that the use of very small doses of testosterone by mouth, as methyl testosterone five mgm. daily, when given for two or three months, almost always produces mild degrees of virilism. It appears that the use of testosterone over a short period of time for an individual episode of bleeding is useful and harmless, but that its prolonged use is not desirable because of even mild virilization.

For dysmenorrhea, the androgens have been used, on the one hand to interrupt ovulation if given in sufficient amount in the week preceding ovulation, but also apparently there is decreased pain if methyl testosterone ten mgm. daily for six days is prescribed immediately following the menstrual period. Usually this does not interfere with ovulation, but menstrual pain may be improved. The explanation is not clear.

For frigidity, a minority have used androgens, as injections, or as a local testosterone cream to the clitoris. It is quite evident that sufficient testosterone will cause growth of the clitoris, and evidently increased sexual stimulation of this organ. More often, the emphasis is placed on the psychological aspect in the treatment of frigidity than on the use of androgens.

For endometriosis, a few have used small doses of methyl testosterone, as five or ten mgm. daily for three months at the time, with reports of decrease or the disappearance of the endometrial implants. While some are enthusiastic regarding this treatment, others believe it has little or no value.

For osteoporosis in the elderly, the use of testosterone alone or in combination with estrogens apparently aids in the recalcification of demineralized bones with relief of bone pain and general improvement in the well-being of the patient. This hormone treatment, singly or in combination, is being widely used in geriatrics, undoubtedly with good effect.

The use of androgens in gynecology is not a wide one.

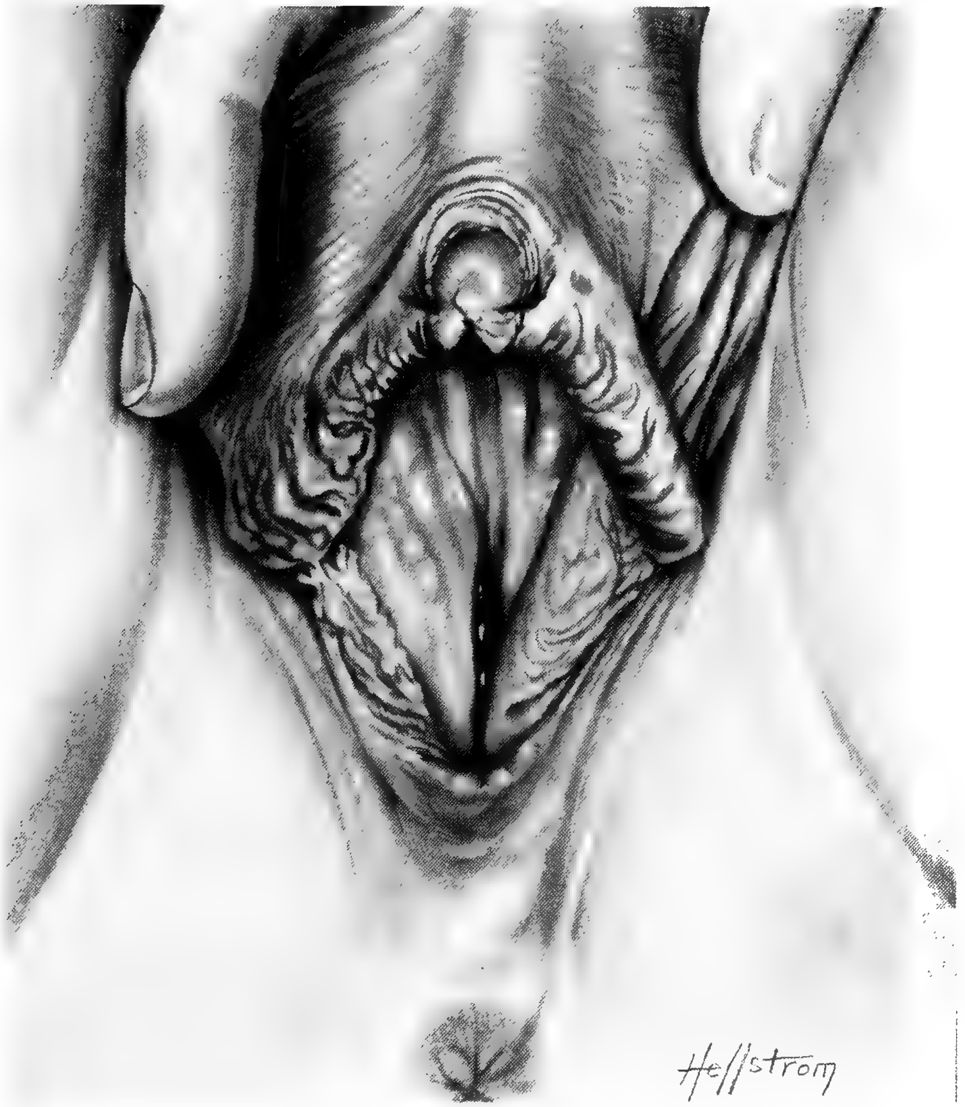


Fig. 7. Hypertrophy of the clitoris and prepuce, caused by testosterone therapy. The patient, age 16 years, had had pubertal metrorrhagia for two years, treated by a number of intramuscular administrations of testosterone propionate. Also a slight mustache had formed, and there was slight acne. Better results followed progesterone therapy given each month over a three to five day duration only.

ASSAY OF HORMONES

Estrogens

The assay of estrogens continues to be a difficult problem for clinical application. The Smith and Smith method from 1938 involved the extraction of estrogens from a large sample of urine with benzene in a complicated manner over a period of twenty-four hours. Finally the three estrogens, estrone, estriol and estradiol were fractionated and determined quantitatively by injection of the extracts into castrated adult female rats. The smallest amount that would produce a full estrogenic effect in the vaginal smear of the rat represented one rat unit. This method is so time-consuming that is is impractical for ordinary clinical use, and yet is probably the best method available today. Since then colorimetric methods have been developed but these are variable and apparently inaccurate. Chromatographic methods are being developed, and perhaps will be the simple approach to the quantitative study of estrogenic hormone on a clinical basis.

Progesterone and Pregnandiol

The assay for progesterone is an impractical one for clinical use. It is performed by injecting extracts from urine or serum into castrated female rabbits which have been primed with a proper amount of estrogen. Later histologic sections are made from the excised uteri. The smallest amount of the extract that will produce a progestational change in the endometrium of the rabbit represents one rabbit unit. This method of analysis was an early development in the study of progestins, which represented unpurified progesterone in extracts. Later, one rabbit unit coincidentally proved to represent the effect of one milligram of pure progesterone. The present method of studying progesterone in the human is the determination of pregnandiol excretion in the urine. This excretion product or metabolic derivative of progesterone represents from thirty per cent to fifty per cent of the original progesterone present. The fate of the remainder of the progesterone and its method of metabolization are unknown. However, pregnandiol determinations at first by weight and now by colorimetric methods, have been helpful in elucidating the presence of progesterone in various clinical conditions. In the majority of cases with threatened abortion or incomplete abortion, the pregnandiol values are normal until the pregnancy is obviously being disengaged. In a very occasional case with threatened abortion pregnandiol studies may show a diminished excretion of this material, which would seem to indicate the presence of a subnormal amount of progesterone. The administration of progesterone in such unusual instances apparently is of value in those cases.

Follicle Stimulating Hormone

The follicle stimulating hormone, known as FSH, is determined by extracting urine or blood serum, precipitating the hormone by the addition of alcohol, washing the precipitate with ether, and re-dissolving in a small amount of water. The material is then injected into immature mice or rats of nineteen to twenty-one days of age. After four days the animals are sacrificed and the ovaries are studied microscopically. The smallest amount of extract that will produce well-formed follicles represents one mouse or one rat unit. The determination of this hormone has been considered of importance in the study of amenorrhea, an excess amount of FSH indicating gonadal failure, and a deficient amount of FSH representing pituitary failure. In abnormal bleeding cases, particularly associated with endometrial hyperplasia, one expects to find increased amounts of FSH because the ovaries presumably have been over-stimulated in the formation of multiple follicles. However, in bleeding cases the FSH may be low or high or more often normal, so that the test is of no value in these instances. After the true menopause has occurred, and the ovaries have become atrophic and insensitive to stimulation, there is a great increase in FSH production by the pituitary gland, apparently because the pituitary gland is not being depressed by estrogen from the ovary. This increased FSH is sometimes known as the menopausal hormone. Its determination is of no clinical value because the ovarian function may be determined readily by inspection of the vagina and the study of vaginal smears.

Luteinizing Hormone

The luteinizing hormone, or LH, is secreted by the pituitary gland a short time before ovulation occurs and continues to be excreted or secreted throughout the remainder of the cycle. This hormone is thought to be responsible for the process of ovulation. The increase in weight of the ventral prostate of hypophysectomized male rats following injection of kaolin extracts of urine determines the rat units present.

Luteotrophic Hormone

Luteotrophic hormone, known as LTH, is secreted by the pituitary gland in the last half of the menstrual cycle and presumably is responsible for the ability of the corpus luteum to produce progesterone. This hormone is thought to be similar or identical to the lactogenic hormone which appears in increasing amounts after delivery and produces lactation in the breasts. Its determination is not practical for clinical use.

Chorionic Gonadotrophin

Chorionic gonadotrophin, on the other hand, is determined with relative ease and great accuracy. This hormone, secreted by the placenta, actually by the Langhans' cells of the chorionic villi, has a gonadotrophic effect very similar to that of FSH, but has this effect only if the experimental animal or individual host has an intact and normally functioning pituitary gland. Chorionic gonadotrophin has both a follicle stimulating factor and a corpus luteum stimulating factor. The former represents about ten or twenty per cent of the chorionic gonadotrophin whereas the luteinizing factor represents eighty or ninety percent of the total. The original method of determining what proved to be chorionic gonadotrophin and not the true pituitary hormones, was the Aschheim-Zondek test in which small portions of urine were injected into immature mice or rats three times daily for two days, after which the animals were sacrificed in four days and the ovaries were studied by histologic section. This remains the best method of determining accurately the amount of chorionic gonadotrophin. Gross determination of the presence of chorionic gonadotrophin are used as a pregnancy test.

The first pregnancy test was the standard Aschheim-Zondek test performed on immature mice and rats. This test required a week or longer because of the necessity of making histologic sections, in addition to waiting four days for the effect on the animal. In the early 1930's, Friedman and Lapham reported the use of rabbits for the determination of pregnancy. Isolated female rabbits, from three to four months of age, when injected intravenously with urine, develop hemorrhagic follicles in the ovaries, as noted by gross appearance, after twenty-four to forty-eight hours. In the adult female rabbit, if completely isolated for a period of three weeks, the intravenous injection of urine produces "Blutpunkte," or blood points, indicating multiple ovulations in the ovaries, usually two to four ovulation points in each ovary, found twenty-four hours following the injection of the urine. The rabbits may be used a number of times, exposing the ovaries through an abdominal or flank incision and inspecting them for gonadotrophic effects. The Friedman test is quite satisfactory, although it does mean the maintainance of a rabbit colony and considerable effort and expense.

Subsequently the rat hyperemia test became available. In this method specimens of urine or serum are injected into the immature rat and the ovaries are inspected from six to twenty-four hours later. A change in color of the ovaries is determined by their comparison with a color chart. This test has been quite accurate in the hands of some observers, but difficult to interpret with others. Frog tests became popular in about 1946. First the South African female toad (Xenopus laevis) was found to extrude eggs within a few hours after injecting urine from a pregnant woman into the dorsal lymph sac. The urine may have been concentrated by precipitation with alcohol, washing with ether and re-dissolving the precipitate in water. These large female toads are expensive to purchase but have the advantage of giving a reasonably accurate result within six hours. More recently, the small male American green tree frog, known as Rana Pipiens, has been used most extensively. An extract of urine is injected into the dorsal lymph sac and the urine from the bladder is examined under the microscope for spermatozoa at intervals of thirty minutes up to four hours. If spermatozoa appear, the test is positive. Apparently there have been some false positive tests in the spring of the year (the mating season), but as a rule this is an exceedingly accurate test for relatively small amounts of chorionic gonadotrophin.

17-Ketosteroids

The determination of 17-ketosteroids is performed by colorimetric analysis. The 17-ketosteroids are end-products of testicular and adrenal cortical hormones. Generally they are a measure of adreno-cortical activity, certainly so in women. The normal values excreted in the urine in women vary from three to four milligrams to twelve milligrams in twenty-four hours. In children the values are two to four milligrams. With degrees of adrenal cortical hyperplasia and hypersecretion of the various adrenal cortical hormones, particularly the androgenic hormone, the determination of the 17-ketosteroids is of great importance. They are elevated not only in adrenal hyperplasia, but also in adrenal cortical tumors, whether benign or malignant, and also in varying degree with the arrhenoblastoma of the ovary. The 17-ketosteroids of late are being studied by chromatography.

11-oxysteroids and 17-hydroxycorticoids

The 11-oxysteroids and 17-hydroxycorticoids (which includes both compound E and compound F) are of importance in a determination when it is necessary to decide if the 17-ketosteroid excretion is from the gonads or from the adrenal glands. First one obtains the 17-ketosteroid determination, then the 11-oxysteroids and the 17-hydroxycorticoids. The latter values are subtracted from the 17-ketosteroids, and the difference represents the androgenic excretion from the extra-adrenal origin. These steroids are also being determined chromatographically. Many different steroids which are intermediate compounds in the synthesis of cortisone, apparently caused by genetic blocks in the synthesis process, are being found by paper chromatography. Their interpretation and quantitative relationship are difficult to assess.

Pregnantriol

Pregnantriol is an end-product of adrenal steroid metabolism and probably is the result of the failure of the adrenal to convert the 17-hydroxyprogesterone to 17-hydroxycorticosterone. It is always present in the adrenogenital syndrome and is of greater value in diagnosis than the 17-ketosteroids. The normal varies from zero to 1.8 milligrams per twenty-four hours. High values are four to six milligrams in infants, twenty-five to forty milligrams in children, and as high as sixty milligrams in adults.

Aldosterone

Aldosterone, known as electrocortin, regulates electrolyte balance and is responsible for the retention of sodium and the excretion of potassium. This property was formerly thought to be under the control of desoxycorticosterone acetate, DCA. However, it now appears that aldosterone is from twenty to one hundred and twenty times more active than DCA.

ACTH

Adrenocorticotropic hormone, ACTH, may be determined by extracting the urine or serum and injecting the material into hypophysectomized rats to determine the effect on the adrenal glands.

Thyroid

The most accurate method at the moment of determining the amount of thyroid hormone, tri-iodothyronine, in the blood, is by determining the protein-bound iodine. While apparently this is an accurate indication of the amount of thyroid hormone present, it is well known that if the patient has ingested any iodine compound in recent months or has had any radiologic examination requiring iodine compounds, such as a gall bladder series or intravenous pyelogram, the protein-bound iodine may be elevated and not represent hormone. Especially is this error frequent in mild degrees of hypothyroidism. A better method is needed.

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CHAPTER III

Diseases of the Vulva

The vulva, representing the external genitalia of the woman, has several component parts: the mons veneris (the fat pad above the symphysis pubis), the labia majora, the labia minora, prepuce, clitoris, vestibule with its urethral meatus, hymen, Skene's ducts, Bartholin glands, and the fourchette. The labia majora are composed of folds of fat, with a connective tissue layer which corresponds to the dartos of the scrotum. It is rich in hair follicles, sebaceous and sudoriparous glands. The labia minora have less cornification of the surface than does ordinary skin and has some smooth muscle which simulates erectile tissue. The sebaceous glands are very numerous, the sudoriparous glands few in number. The inner surfaces of the labia minora blend with the mucous membrane of the vestibule. This transition area is known as the mucocutaneous border. The clitoris contains erectile tissue, and has two vestibular bulbs, corresponding to the corpora spongiosa in the male. These extend to the sides of the vestibule and vagina.

The vulva, because of its varying epithelial forms, shielded position from light and air, friction from clothing and motion, body heat and moisture, sensitivity to hormones and vitamins, developmental anomalies, and susceptibility to specific infections transmitted by sexual intercourse, is involved frequently in inflammatory and trophic diseases of clinical importance.

VENEREAL DISEASE

Fifteen years ago or longer venereal diseases (by definition, transmitted by sexual contact) were of great importance because of their frequency, but the wide-spread use of antibiotic drugs has diminished their incidence materially. It is becoming difficult to find characteristic examples of these diseases for demonstration to students. Though less frequent, proper diagnosis and specific treatment are important to the individual. In the voluminous and fascinating literature on the subject these diseases have been numbered, as the first, the second, third, fourth, fifth, sixth and seventh venereal diseases, although with some difference in order from one author to another.

SYPHILIS

Syphilis, for centuries accepted as the first venereal disease appears in primary, secondary and tertiary forms. The primary, or hard chancre, is a flat greyish ulcer, one or two centimeters in diameter. It may be picked up from the soft skin to demonstrate its firm consistency, and occurs on the labia minora, or inner surface of the labia majora, or on the prepuce. When one or two chancres occur on the contralateral lip at similar level, they are known as kissing chancres, and apparently represent an auto-inocculation. Rarely, the chancre occurs on the vaginal wall, and on the cervix as an erosion, usually eccentrically situated. The diagnosis of these internal chancres is difficult, because the index of suspicion is low and the appearance is not characteristic. Because the chancre appears in the first six weeks of a syphilitic infection and the complement fixation and serologic tests devised by Wasserman, Kahn, and some other more recent ones are not yet reactive, positive diagnosis depends upon demonstration of the sphirochetes by dark-field examination. The technique for this is becoming almost extinct, although every student should have this method demonstrated to him. It consists of gentle drying and cleaning of the ulcer, allowing serum to exude, and the study of the serum under the cover slip with dark-field illumination. The presence of motile spirochetes, with the twenty to thirty spirals characteristic of the Treponema pallida, is considered diagnostic of primary syphilis. The infrequency of the lesion, unfamiliarity with the operation of the dark-field attachments,

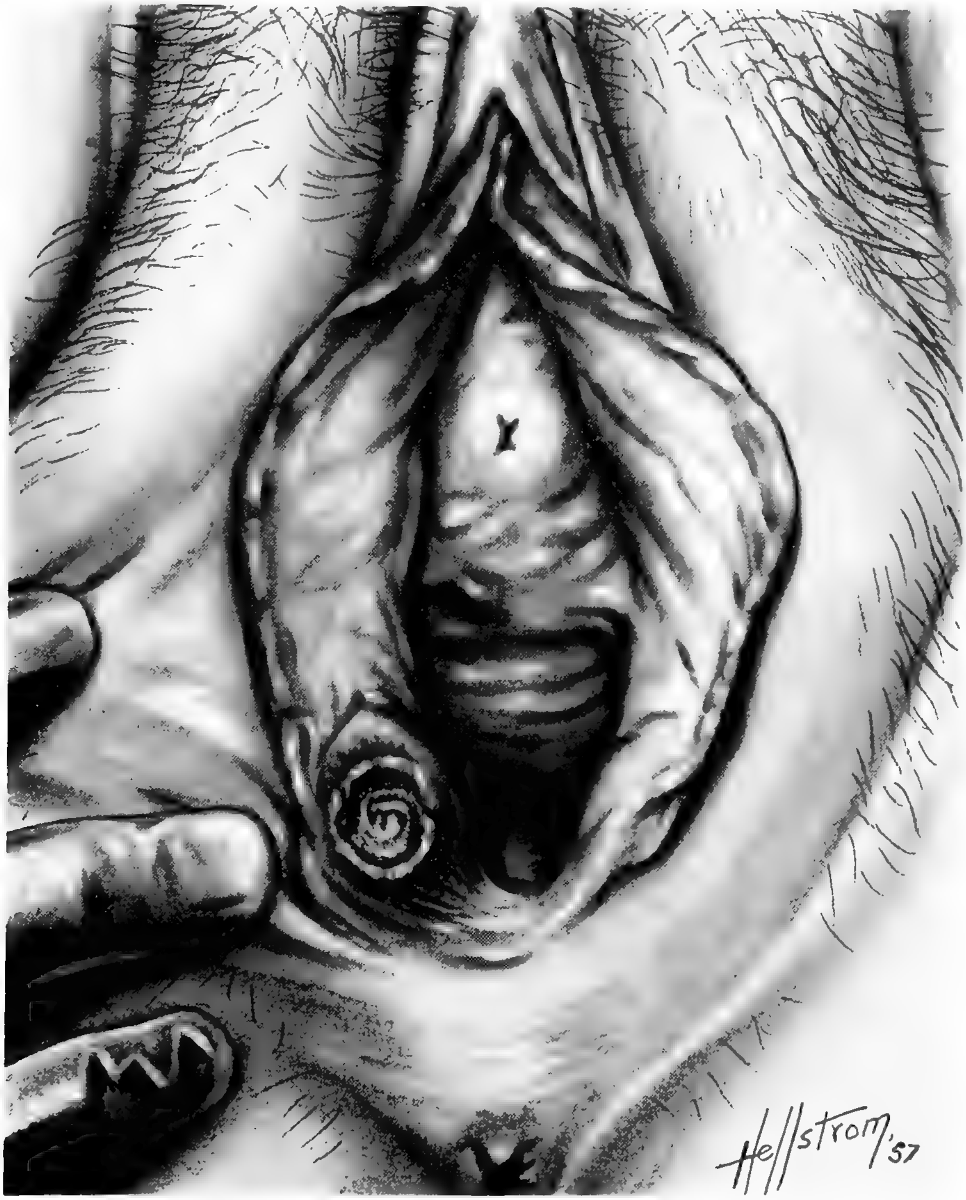


Fig. 8. Chancre, right labium minor. Grayish ulcer, with quite firm edges. Dark-field showed spirochetes of syphilis.

lack of suspicion, and the difficulty of obtaining serum from the poorly accessible lesion on the vagina or cervix, are common causes for failing to make a correct diagnosis. Accurate diagnosis is essential before treatment is started.

Secondary lesions, known as the mucous patch and condyloma latum, usually develop about six weeks after initial infection. The former appear as multiple small, red, raised papules or minute reddish-grey ulcers, which occasionally become confluent. The condyloma latum, usually multiple, has an appearance similar to the hard chancre, but is often larger, oval-shaped, two to three centimeters long, with flat grey base, occurring on the labia minora and majora, and sometimes about the anus. Usually the complement fixation tests are positive by the time the secondary manifestations appear. The dark-field examination usually is positive in the secondary lesions also.

The tertiary lesion, or gumma, occurs even more rarely in the vulva. It is a deep, destructive ulcer with indurated thick edges and base, usually without demonstrable spirochetes, and is diagnosed by exclusion of other diseases (by performing the tests mentioned later and by biopsy) and with positive blood complement fixation tests. The long latent period which elapses before the tertiary lesion becomes manifest, and also the cryptic location of the primary chancre tends to obscure the diagnosis.

The histologic appearance of syphilis is that of a severe non-specific inflammation, particularly with perivascular round cell infiltration (of suggestive but not diagnostic importance) in the chancre and condyloma latum. The gumma is a deep-seated caseous lesion surrounded by fibroid granulation tissue.

As recently as fifteen years ago, the treatment of syphilis depended on the prolonged intravenous injections of arsphenamine (Ehrlich's famous "606"), and its later modifications, at weekly or biweekly intervals, supplemented by intermittent intramuscular injections of bismuth, for one, two or more years. Even then, cure was uncertain. Now, penicillin given in massive doses apparently destroys the Treponema pallida in one week. This seems a miracle to those of us who used to contend with the extremely resistant and persistent spirochete when treated by the old regimes of arsenicals and bismuth. Careful re-appraisal of the result of treatment of this serious systemic disease must be made for another twenty years before we can accept the miracle of penicillin therapy.

An important part of the practice of medicine today is the premarital examination for the particular purpose of discovering venereal disease. The routine use of the V. D. R. L. serologic test for syphilis, which is very sensitive, will point out the case with latent syphilis, when there is no history of or notable lesion to be seen. The clinical pathologist makes a great contribution in the performance of this routine screening test.

GONORRHEA

The second venereal disease also has a history of antiquity. Easily acquired and universal in geographic distribution, it can be controlled by antibiotic therapy. Eventually it may virtually disappear from communities with a well-regulated health regime. In the adult, the causal gram-negative biscuit-shaped diplococci (Neisseria) delight in living within the neutrophil leukocytes, attack the Skene's ducts of the urethra, the Bartholin's glands of the vestibule, the cervix, the Fallopian tubes, ovaries and peritoneum. This purulent, non-ulcerative disease in the adult is transmitted only by sexual intercourse. The infection has greatly decreased in the past ten years, according to United States Public Health reports, and is distinctly uncommon in private practice. Yet the possibility of its occurrence must be kept constantly in mind when pelvic infection is present. Skene's ducts

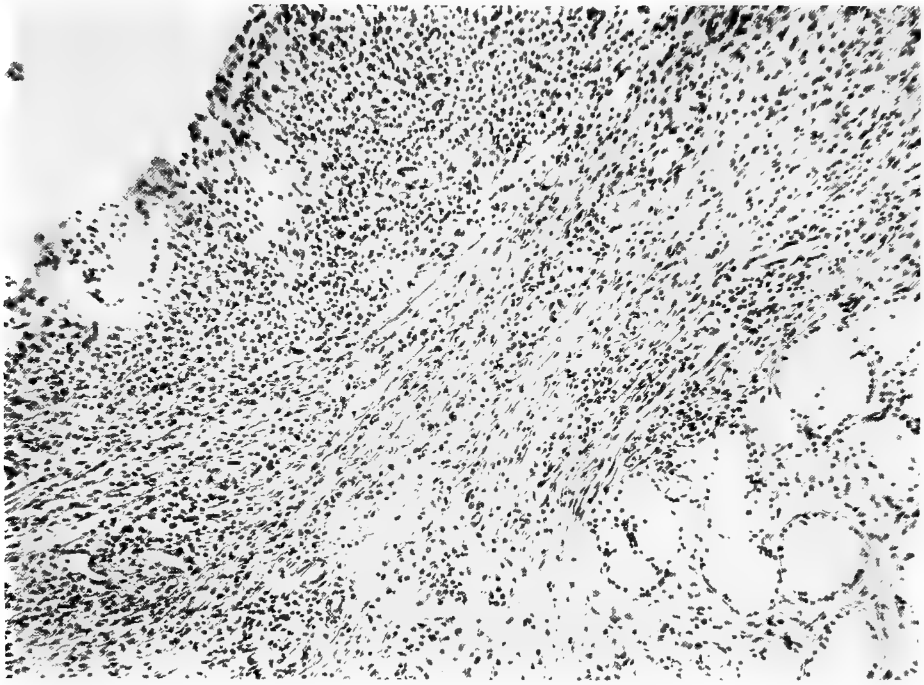


Fig. 9. Bartholin's gland abscess. The interior of the abcess wall is composed of polymorphonuclear leucocytes, lymphocytes, exudate, and an imperfect lining of glandular epithelium or transitional epithelial cells. The wall of the abscess contains newly-formed fibrous tissue, with inflammatory cells which extends less about a deeper portion of the Bartholin's gland.

have two minute openings on the inferior margin of the urethral meatus; these may be recognized by careful inspection. These tubules with finger-like projections are lined with transitional epithelium, with a surface of cuboidal or low columnar epithelium in a single layer above stratified squamous-like cells, the latter simulating the reserve cells in the cervix, or the deeper intermediate layers of squamous epithelium.

There are many smaller and variable ducts along the course of the urethra; these have been reconstructed and described in detail by Huffman. The smaller and more deep seated ducts are less susceptible to invasion by the gonococcus. Acute gonorrhea commonly is accompanied by a burning sensation on urination and increased frequency of voiding. The meatus appears reddened, and a drop or two of yellow, purulent secretion may be milked from the tender urethra. For many years after the acute stage, a mucopurulent discharge may be milked from the urethra and Skene's ducts; gonococci have been recovered repeatedly from this exudate. For this reason, it is commonly taught that any chronic discharge from Skene's ducts is presumptious evidence of preceding acute gonorrhea. However, this is not the case. Chronic discharge from Skene's ducts is frequent in patients who have never had gonorrhea, and is most often related to the trichomonas vaginalis, an extremely common inhabitant of the vagina. The gonococcus is usually eradicated with one or two injections of penicillin, and is susceptible to a majority of the other antibiotics.

Bartholin's gland is the tubular racemose (finger-like) gland situated in each labium major. Its duct opens into the vestibule near the center and just external to the hymen on each side. Its orifice may be seen by close inspection. This small soft gland is not palpable in its normal state. It secretes an alkaline mucus, which exudes in varying amount with

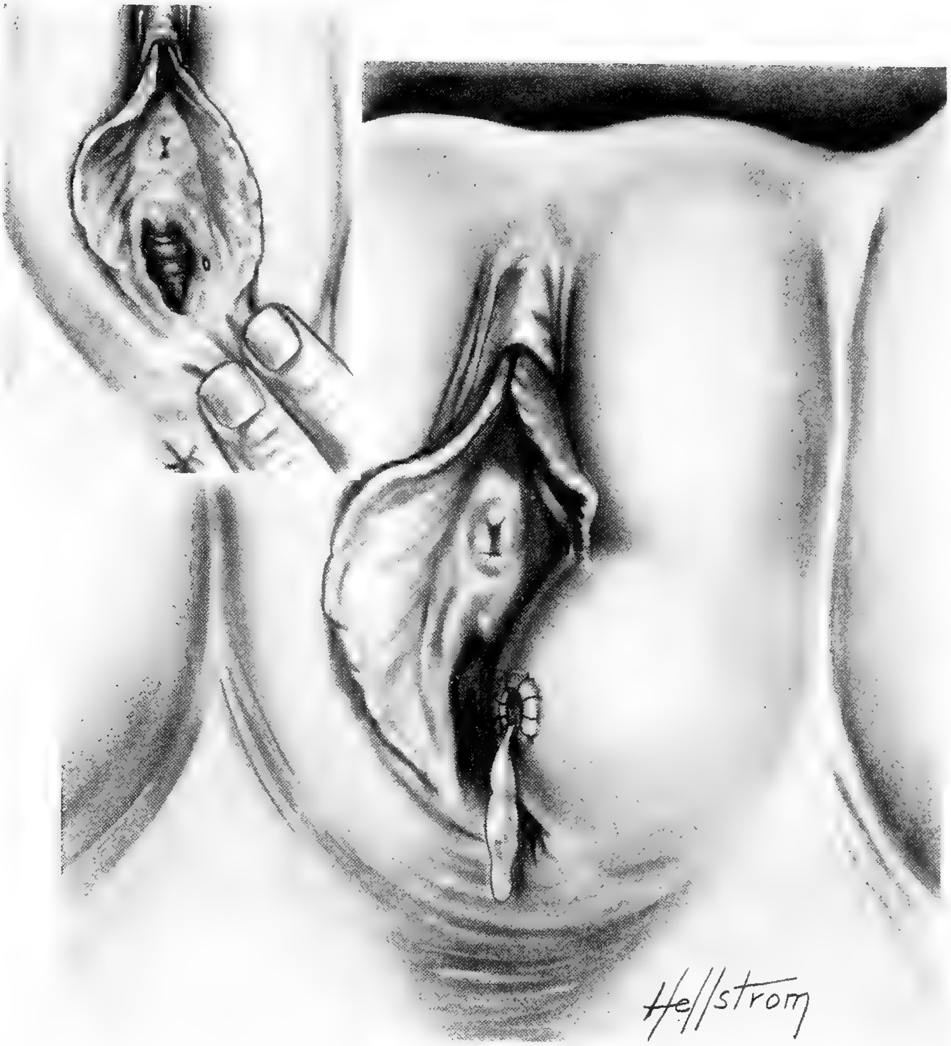


Fig. 10. Fenestration or marsupialization of Bartholin's gland cyst or abscess. The lining is sutured to the muco-cutaneous border; drain is removed after 48 hours. The opening may contract considerably, and the gland may function normally.

sexual stimulation. The gonococcus thrives in this medium (in contrast to the acid vagina), causes exudation of polymorphs into the lumen, and severe acute inflammation about the ducts and tubules, producing obstruction of a major duct and an abscess. Other bacteria, such as the colon bacillus, appear as secondary invaders, and the gonococcus in this locality quickly dies out. The acute infection usually responds rapidly to penicillin therapy and the pain is alleviated by hot packs or soaks in a tub of plain hot water. The early acute infection usually resolves; if it fails to do so abscesses form and require incision and drainage. Following infiltration with a local anesthetic, a vertical incision is made just external to the hymen; then a small transverse incision helps to maintain the opening. A gauze wick is inserted; this usually falls out that evening in the bath or may be removed in twenty-four hours. More recently, even in the acute stage, some have advocated suture of the abscess wall to the mucocutaneous border, using fine interrupted chromic catgut, maintaining an opening one centimeter in diameter. A wick is left in place for a day or two. A new duct opening tends to form and this allows return of function of the gland, after the infection has disappeared. After the acute infection has subsided, chronic induration, the size of a pea or bean, may be felt deep in the labium major, or a cyst one to four, five or eight centimeters in diameter may develop. Acute abscesses may recur in either the thickened gland or in the cysts, or pain and discomfort from slight recurrence of inflammation may occur during menstruation or after sexual intercourse. If there are no symptoms or recrudescences in the chronic state, no treatment is indicated. With recurrent abscess, recurrent pain and dyspareunia, excision is the best procedure. Recently, several gynecologists have stressed the fenestration operation for cysts, incising and suturing the wall of the cyst to the mucocutaneous border just external to the hymen, making an opening one centimeter in diameter, which later shrinks to one, two or three millimeters. The logic of this procedure lies in the fact that most cysts are duct cysts, lined by transitional epithelium, and the restoration of a new duct opening may produce normal function. Two complications may influence the final result of this treatment. If the new opening later forms a stricture, recurrent cyst and infection will likely follow. The second is that beneath every cyst the remaining gland tubules are involved in thickened scar tissue with chronic inflammation, which may obliterate their continuity and cause recurrent symptoms. Excision, when symptomatically necessary, has produced good results. This minor operation may prove to be a major procedure and should never be done as an office procedure because of the great vascularity of this area. The numerous arteries and the venous plexes require numerous fine catgut ligatures and multiple sutures to close the cavity which is apt to extend deeper than anticipated. The

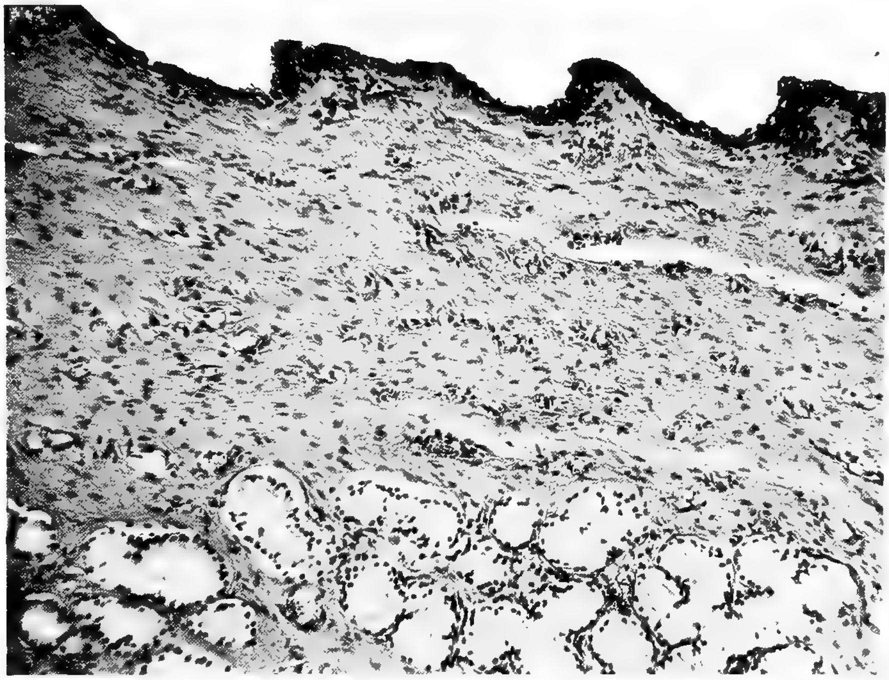


Fig. 11. Bartholin's gland cyst. The cyst lining of transitional epithelium is seen at the top of the photograph. There are several layers of squamous-like cells covered with a single layer of cuboidal epithelial cells. Deeper in the cyst wall is the typical appearance of the Bartholin's gland, a tubular racemose formation containing a single layer of cuboidal epithelial cells with clear or faintly bluish staining cytoplasm and basal nuclei. This gland has a very distinctive appearance. Occasionally the cysts may be lined by the cuboidal glandular epithelium, but as a rule they are lined by the transitional duct epithelium.

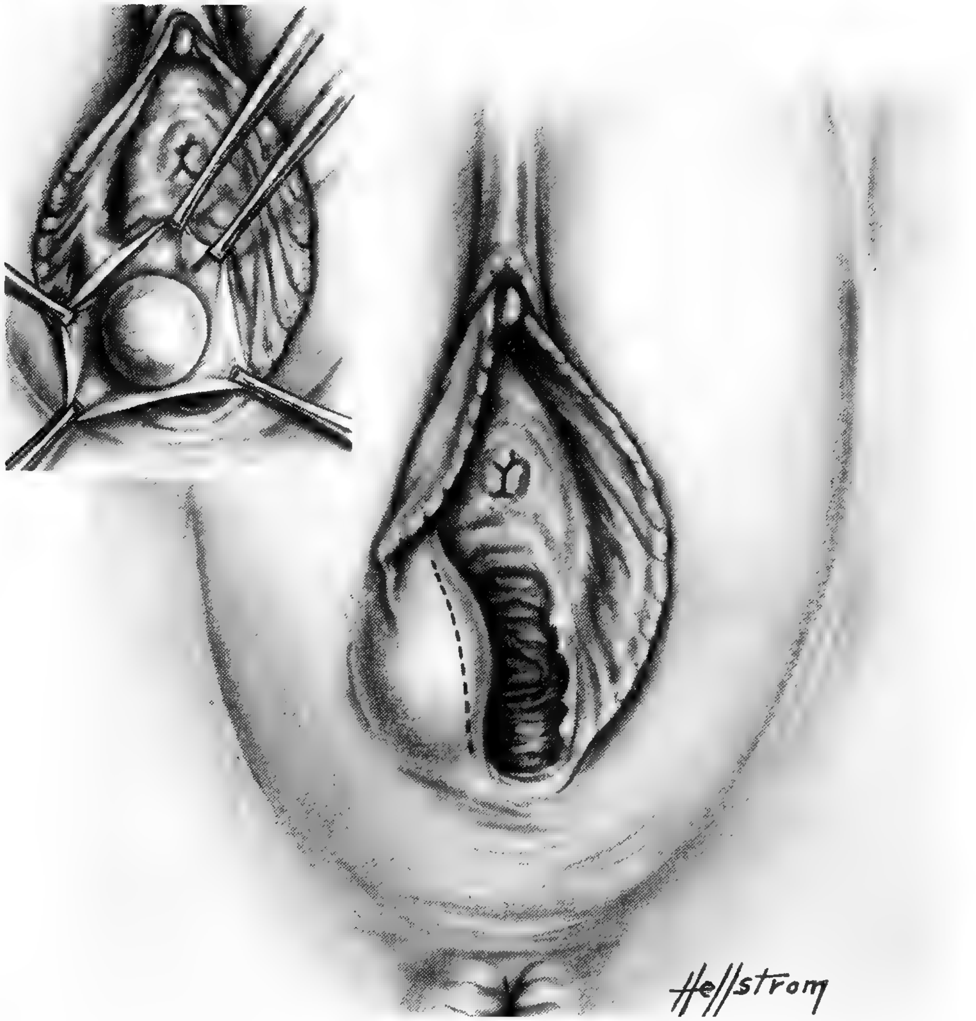


Fig. 12. Bartholin's gland cyst. When associated with pain, soreness, dyspareunia or recurrent infection, it may be excised. Deep to the cyst the gland usually shows marked thickening. Commonly the cyst is broken during removal, and clear mucus is spilled. Sometimes the fluid is purulent, and a small drain may be advisable in the closure.

rectum has been injured occasionally in the course of the excision, with the formation of a rectovaginal fistula which is difficult to correct. As a rule the loss of these lubricating glands causes no symptoms, but occasionally the patient does have some dryness and dyspareunia, and may require a lubricating jelly. As with Skene's duct infection, all Bartholin's gland infections have been considered due to the gonococcus, but this is incorrect. The cyst or small thickened gland is not necessarily evidence of previous gonorrhea, as commonly believed. Many acute and most chronic infections seen in private practice are due to the trichomonas vaginalis, and probably its secondary invader, the colon bacillus. With the acute infection and abscess formation, the colon bacillus becomes the prominent and apparent etiologic agent. The trichomonas vaginalis is not of immediate importance, but for cure and prevention of recurrent infection in the Bartholin glands, Skene's ducts and even recurrent cystitis, prolonged treatment of the trichomonas vaginalis is indicated. More study of the relationship between these various infections is highly desirable. Acute infection of Skene's ducts is cured by penicillin. Chronic infection with other secondary organisms usually is of little clinical importance. The occasional small cyst may be excised. The ducts may be threaded on a curved needle and be completely incised and laid open by the cutting current.

CHANCROID

The third venereal disease is chancroid, soft chancre, or ulcus molle. It begins as a greyish ulcer, similar to the hard chancre of syphilis, but usually is soft in consistency. There may be multiple lesions about the inner surfaces of the labia majora and over the labia minora. The etiologic agent, the gram-negative streptobacillus of Ducrey, appears in smears in characteristic long chains. It invades lymphatics, is carried to the inguinal lymph nodes, where multiple abscesses, buboes, or "blue balls" appear. A brawny edema of the labia, with deeply penetrating destructive ulcers may occur in the late stages. The organism, described by Ducrey before the turn of the century, was extremely difficult to culture until the French succeeded in about 1928, when the commercial *dmelcos* vaccine was produced. This vaccine was used as a diagnostic test, the *dmelcos* test, by producing an intradermal wheal on the forearm. A raised erythematous reaction after twenty-four hours was considered a positive test, and was assumed to mean the patient had or had had chancroid. Wide use of this test, especially among prostitutes, showed that only ten per cent of those with positive tests actually had, or gave a history of the disease, while most men with positive tests showed ulcers or buboes. For this reason, and because of predilection of the disease for males, it was considered that women may be carriers of the infection, without necessarily having clinical chancroid. The vaccine was used in treatment, being given intravenously at weekly intervals. Chills and fever up to 107 degrees were produced. Later the vaccine was produced in this country, and is at present available for diagnostic tests. Chancroid is very responsive to the sulfonamides and this fact has changed its treatment and incidence radically.

GRANULOMA INGUINALE

The fourth venereal disease, granuloma inguinale, is a destructive ulceration of the skin. It destroys the epidermis of the vulva, often extends to the inguinal regions, and in severe cases may involve the entire vulva and peri-anal area. Occasionally it occurs in the mouth and jaw, apparently being contracted there by unusual sexual practices. A few cases of systemic infection, with destructive lesions of bone have been described. Granuloma inguinale occurs almost exclusively in negroes or those of partial negro descent. Brawny edema of the vulva with destructive ulcers may occur and granulomatous ulceration of the cervix, simulating carcinoma, has been described in recent years.

The infective organism is Donovan's bacillus. These minute intracellular organisms appear as grains of pepper within large epithelioid cells or within a large cell membrane with no nucleus, and sometimes have capsules. The nature of the Donovan bodies, whether bacterial, protozoal, or viral inclusions was in doubt until Goodpasture and his associates transmitted the infection to monkeys and fulfilled Koch's postulates by recovering the organisms, growing them in artificial media, and reproducing the infection in human volunteers. The bacterial nature of Donovan bodies now is accepted.

Diagnosis is made by cleaning the ulcer, after which it is scraped gently with the flat belly of a scalpel. The material is smeared on slides and stained with Wright's or

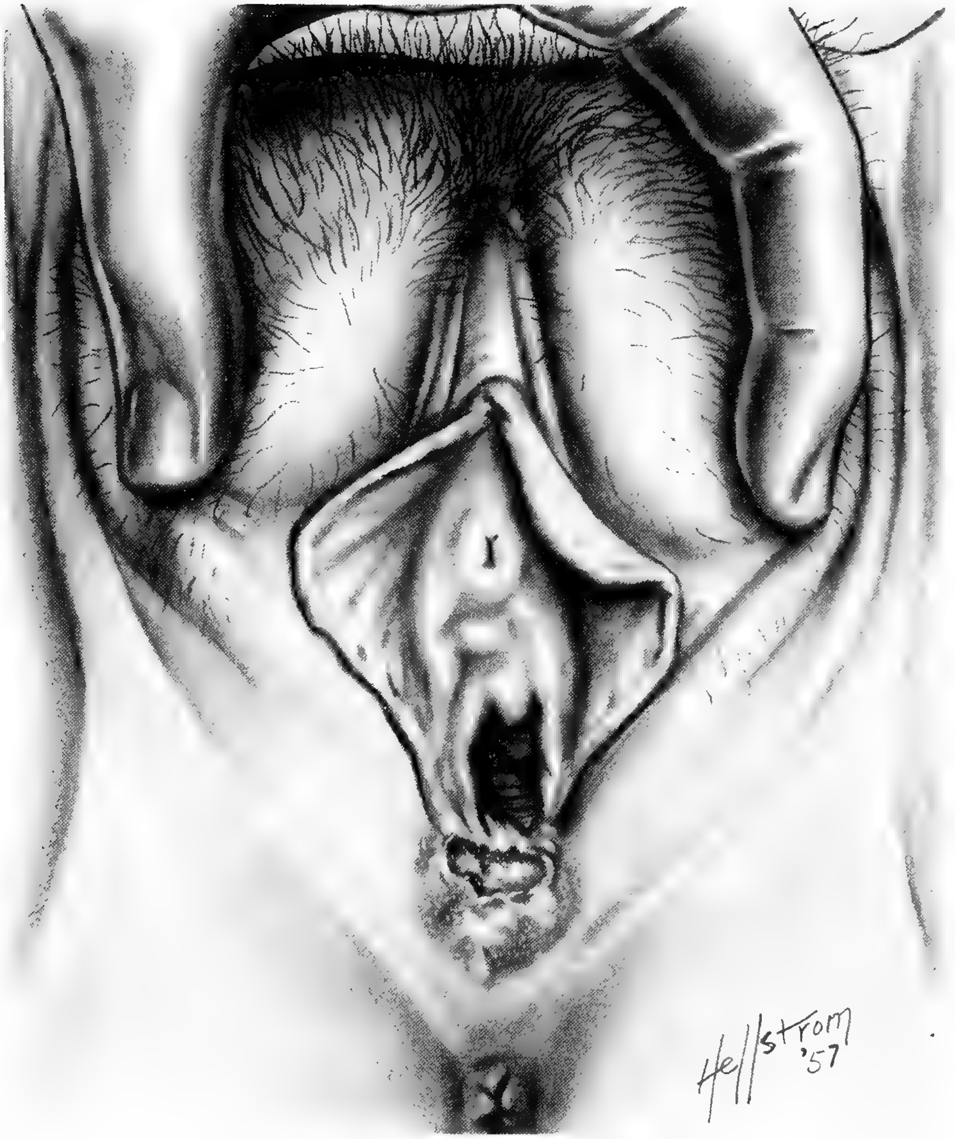
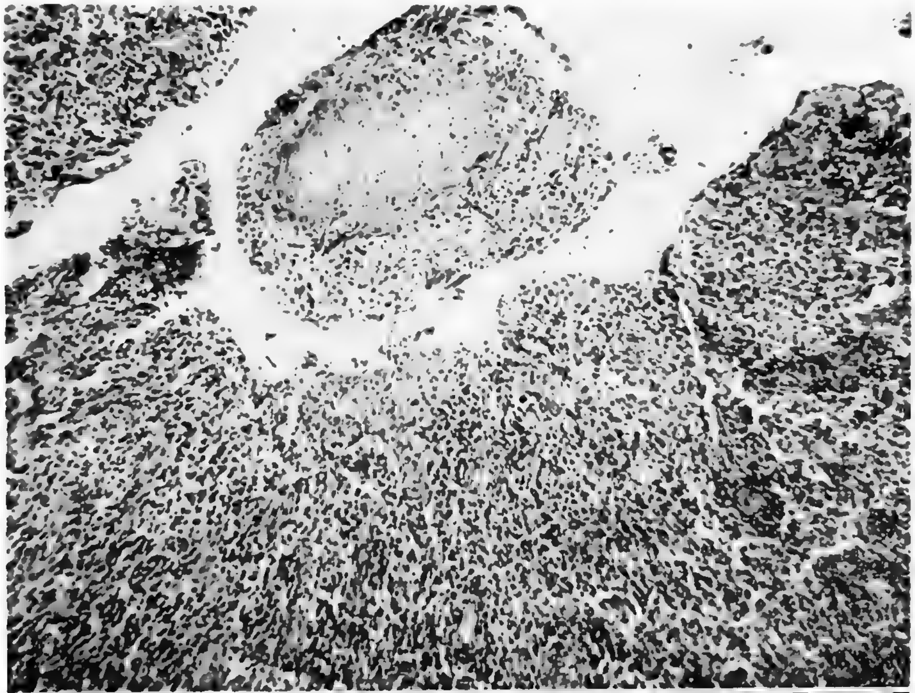


Fig. 13. Chancroid, soft chancre, near fourchette. A dirty grayish, superficial ulcer with irregular border, chronic, painful. It may extend to large ulcerative lesions and be associated with elephantiasis. The Ducrey skin test is positive, and smears may reveal the long chains of gram-negative streptobacilli. Treatment by sulfonamides.

Giemsa's stain. The typical appearance of the pepper-like organisms is diagnostic. Microscopic sections show a severe non-specific chronic inflammation.

For many years the most effective treatment was intravenous injection, at weekly intervals, of one per cent solution of tartar emetic (sodium antimony tartrate). If the patient ceased treatment before complete cure, recurrence and extension of the ulcerative process was followed by diminished response to subsequent injections. Other antimony drugs were useful in the treatment of granuloma inguinale, notably fuadin, named after King Fuad of Egypt, in response to his permission for use of this drug experimentally on his subjects. Now, streptomycin or tetracyline have proven more effective, although the response is not dramatic. Prolonged treatment may be necessary.

Fig. 14. Granuloma inguinale of the vulva. Note the severe subacute and chronic inflammation, represented by lymphocytes and plasma cells, and polymorphonuclear leucocytes also. The upper portion of the photograph shows an area of squamous epithelium which is rather lost in the granulation tissue and evidently has made a valiant effort to try to cover over the destructed surface but to little avail. The appearance of this inflammatory tissue is not specific.



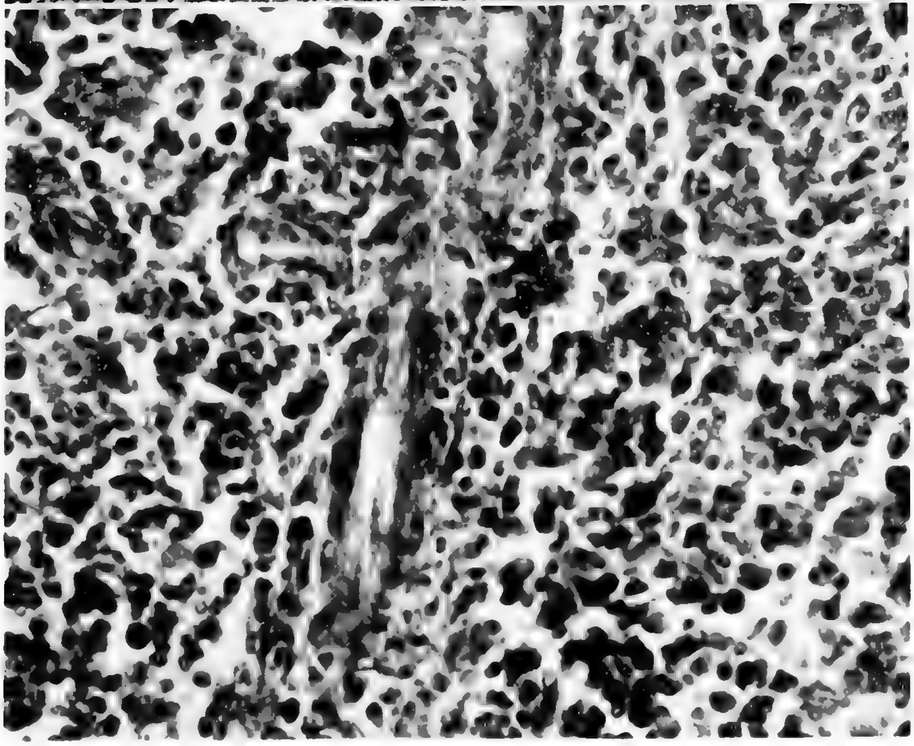
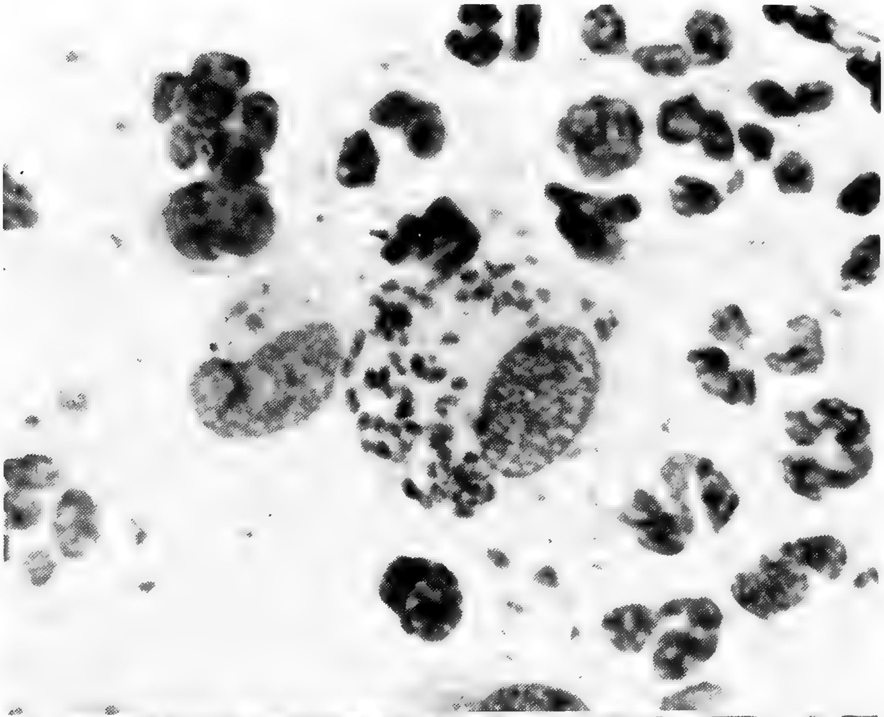


Fig. 15. High power view of granuloma inguinale of vulva, showing closely packed leucocytes, plasma cells and polymorphs. The arterioles show increased connective tissue reaction. Scrapings from the lesion stained with Wright's or Giemsa's stain show Donovan's organisms.

Fig. 16A. Donovan organisms encapsulated and located inside the cell membrane of a large epithelioid cell.



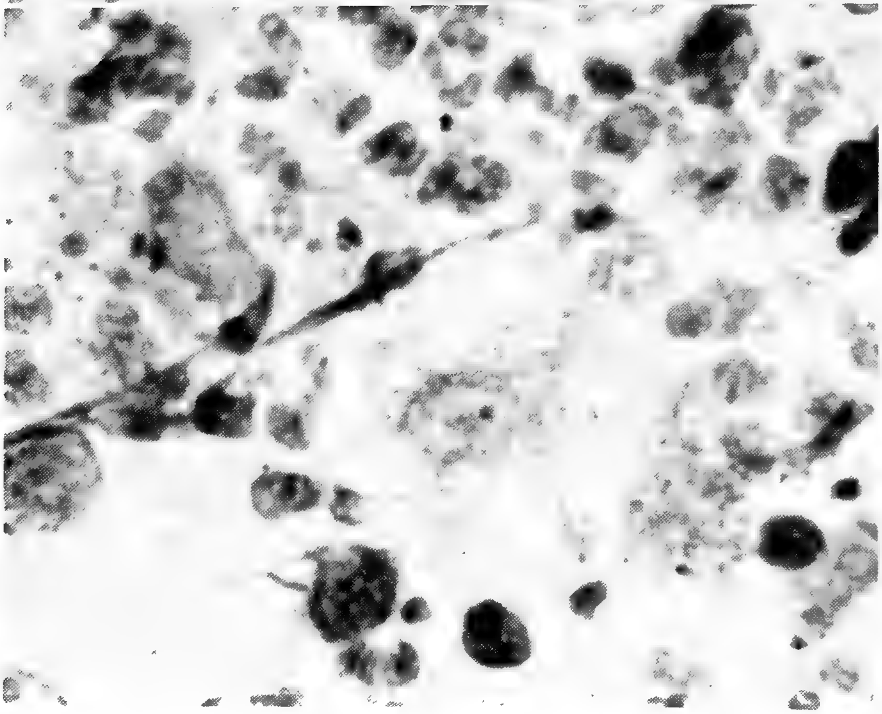


Fig. 16B. Donovan organism without capsules again located within the cell membrane of an epithelioid cell. They are extremely small and difficult to photograph through the oil immersion lens.

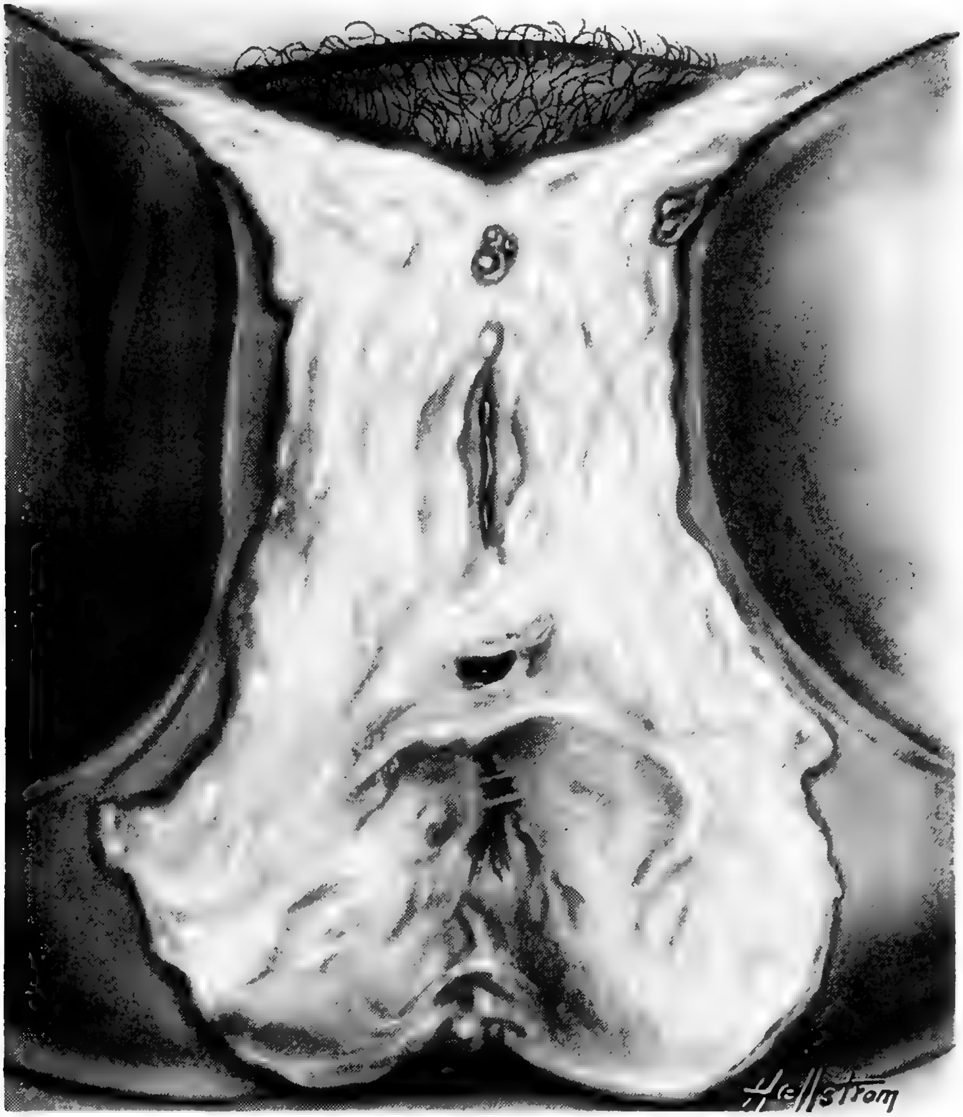


Fig. 17. Granuloma inguinale. An extensive ulcerative destruction of the skin, which has removed the external genitalia. Typically, it extends up into the inguinal areas. The urethra appears as a slit, the vagina as a transverse oval opening, while the rectum opens up between the raw buttocks. The margins are serpiginous, slightly raised, and have increased pigmentation. Scrapings, stained with Wright's or Giemsa's stain, show Donovan's organisms.

LYMPHOGRANULOMA VENEREUM

Lymphogranuloma venereum, also has a romantic history. Known since medieval times it has had many names, including tropical bubo, climatic bubo (because sailors visiting tropical ports were particularly prone to have the disease), and, more recently, lymphogranuloma inguinale and lymphopathia venereum. The disease now is listed only as lymphogranuloma venereum in the *Cumulative Index.*

Wilhelm Frei, in 1925, using pus aspirated from inguinal buboes, devised a skin test which is accepted as diagnostic. Later the virus was isolated. On the basis of experience with the Frei test, it has been established that the disease, in males, usually results in inguinal adenitis and multiple draining sinuses which heal poorly, while in females, it often causes elephantiasis vulvae (esthiomene) and rectal strictures. The disease may begin as a minute ulcer, or chancre, which may be overlooked and may disappear in a few weeks. The organism travels along the lymphatics to the inguinal nodes in men, and by lymphangitis obstructs the channels in the vulva, which produces chronic brawny edema. Deep ulcers occur around the inner surfaces of the vulva. The lymphatics of the lower third of the vulva drain up along the rectum, and are especially numerous about the ampulla. This explains why rectal stricture is common in females. The mucosa of the rectum is thrown up in longitudinal folds, resembling the thick folds of corduroy fabric. An urethral form of this infection, beginning as chronic urethritis, which might progress

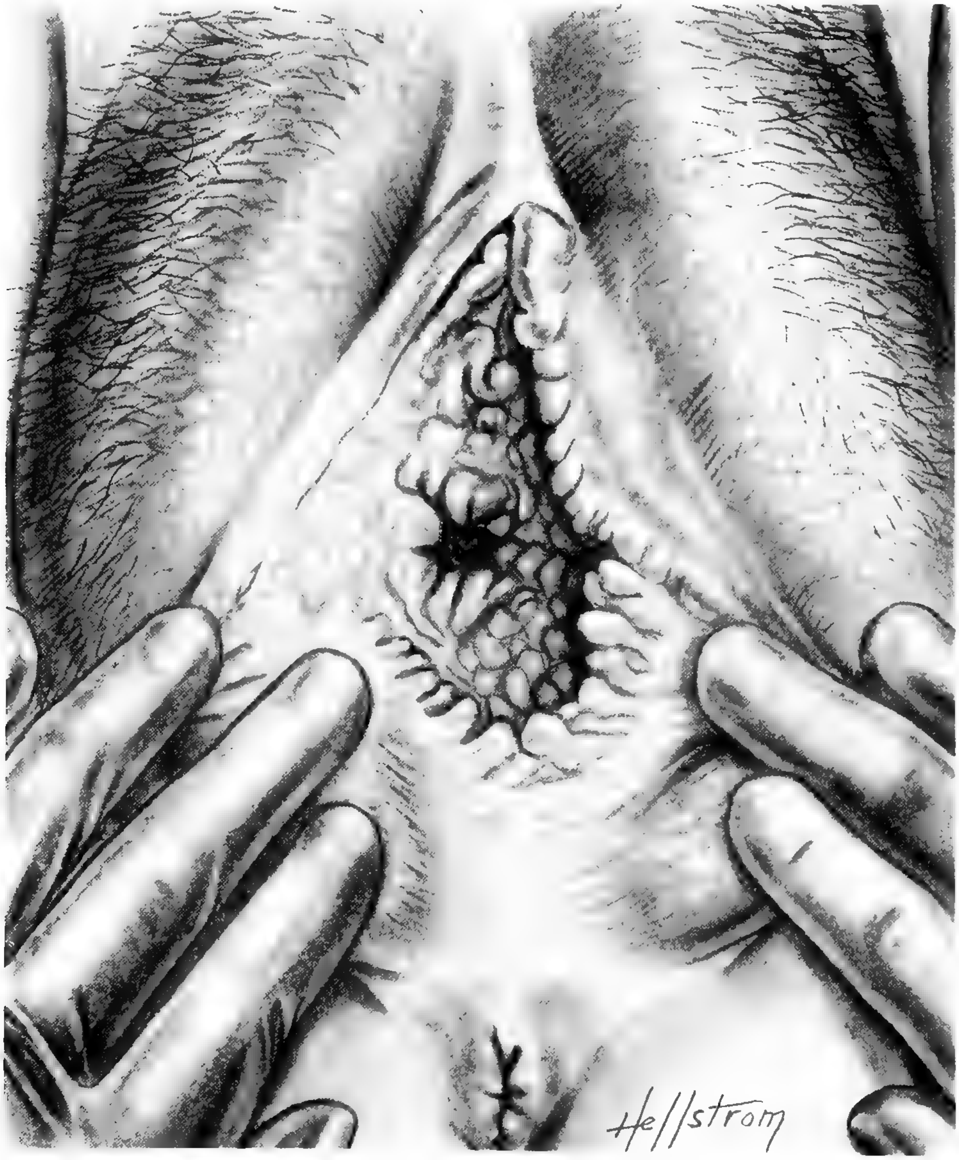


Fig. 18. Lymphogranuloma venereum. Elephantiasis vulvae. Esthiomene. Caused by Frei's filterable virus which blocks the lymphatics and produces severe ulcerative destruction around the vagina, to sides of rectum and of the urethra.

to stricture and retention of urine, or to destructive ulceration of the meatus or entire urethra as far as the internal sphincter, was described by the author in 1936. Varying degrees of incontinence occur in some of these cases. Histologically, this disease appears as a severe non-specific chronic inflammation, with occasional giant cells and a few epitheliod cells. Diagnosis may be confirmed by the Frei test, with antigen which now is manufactured from mouse brain or cultures in the inoculated egg embryo.

Treatment by desensitization with Frei antigen seemed to give some improvement. This has been largely superseded by the use of sulfonamides and aureomycin. The sulfonamides at first were thought to be of value only in aiding secondary infection, but now it appears that they also inhibit the virus to some degree. Aureomycin has seemed helpful. The incidence of the disease is decreasing rapidly in this country. In 1946, the United States Public Health Service reported 2603 cases; in 1955, a similar report listed only 875 cases. Undoubtedly many cases were not reported, but this probably does indicate a significant decrease.

VINCENT'S DISEASE

One form of a rare, deep, and destructive ulcer around the vulva, often associated with varying degrees of chronic hypertrophic vulvitis, is caused by Vincent's organisms, the large, elongated, deeply staining bacillus, and the associated coarse spirillum. Apparently this is similar to Vincent's infection of the mouth, but when it occurs on the vulva, it may be transmitted by sexual intercourse. Diagnosis is made by smears stained by Gram's method. Treatment has been by arsphenamines. It has seemed at times that the organism is a secondary invader.

HERPES GENITALIS

Herpes genitalis has been listed by some as an infection transmitted by sexual intercourse, but the multiple bullae, and when broken, the superficial ulcerative lesions, may occur without sexual contact. If the bullae are broken, diagnosis may be difficult, and the viral nature of the minute, tender ulcers may be unsuspected. Healing usually occurs quickly with cleanliness alone, but recurrence, especially with the menses, may be frequent. The recurrent form is annoying and may be difficult to cure. Dermatologists have used repeated small-pox vaccinations, hoping for transference of viral immunity. Perhaps aureomycin or chloromycetin, may be of value, as they have in some viral diseases, but additional clinical study is needed.

CONDYLOMA ACCUMINATUM

The condyloma accuminatum, or genital wart, long was known as the "venereal wart." Some twenty or thirty years ago it became evident that this virus infection may occur without sexual intercourse, and the term, "venereal wart", is known to be a misnomer. These multiple, spreading, and growing warts may occur without sexual transmission. They may be found in virgin nurses and female medical students. More often, the lesion does seem of venereal origin, since both the male and female partner may have the warts. Formerly, it was associated with gonorrhea; now it occurs much more frequently in private practice than does gonorrhea. The lesion rarely occurs in prepubescent girls or postmenopausal women. It is interesting that during pregnancy the warts

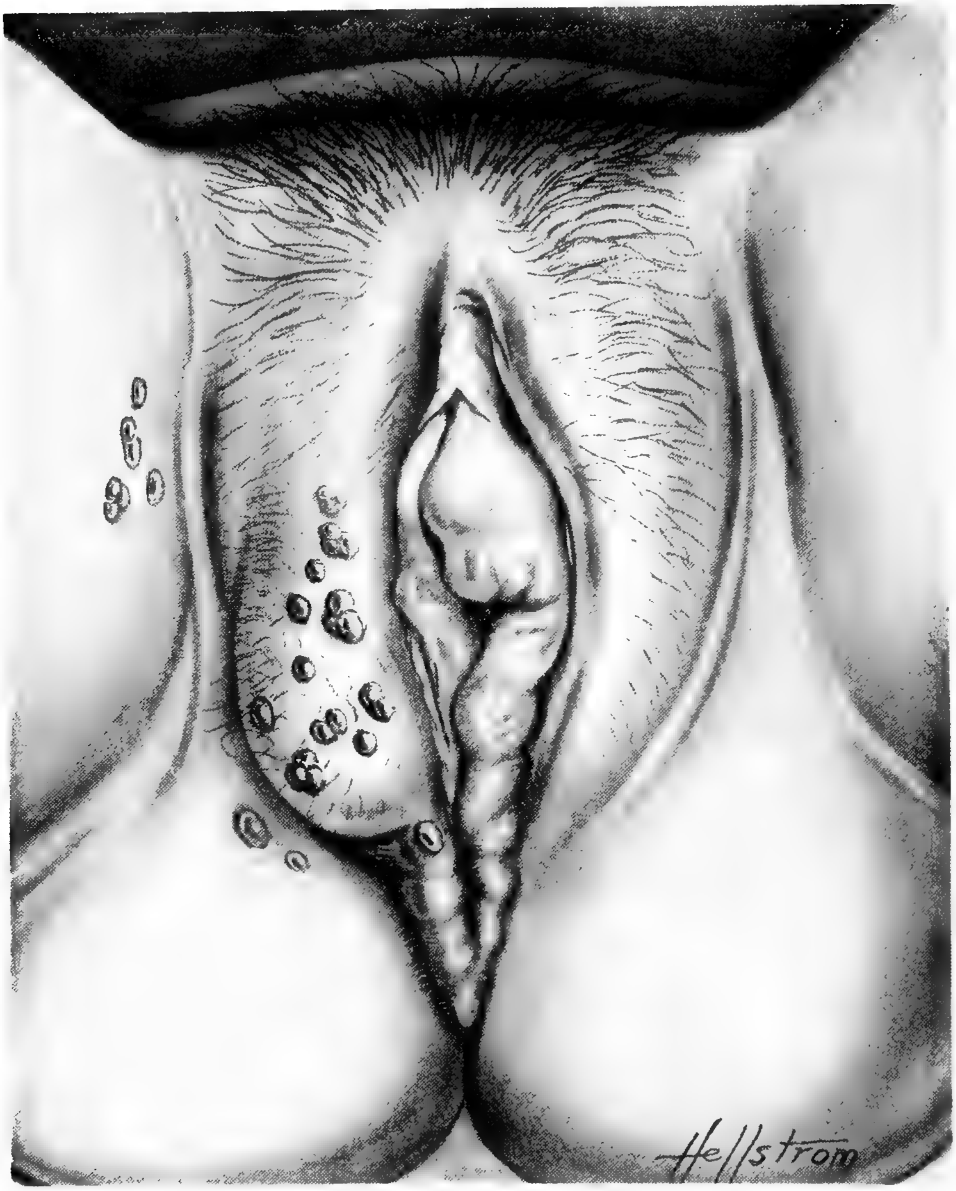


Fig. 19. Herpes genitalis. An infection caused by a filterable virus. Note oedema of right labium major and left labium minor. Blebs or bullae are present over the right labium major and onto the thigh and buttock. Others that have ruptured have left minute ulcers on the labia minora.

may extend over the entire vulva, become very large, and may extend along the vagina and over the cervix. In the non-pregnant, the warts may occur in the vagina or on the cervix, but to a less degree than in pregnant women.

The microscopic appearance is that of very thick stratified squamous epithelium, covering thin elongated connective tissue stalks. Usually the squamous epithelial cells are regular in size and shape and have normal maturity in the superficial layer. Increased number of mitoses indicate increased rate of growth. At times, these warts may have remarkable cellular changes, with continued immaturity up to the surface layer, and with abnormal and atypical nuclei. These changes, especially when found in isolated lesions on the cervix,

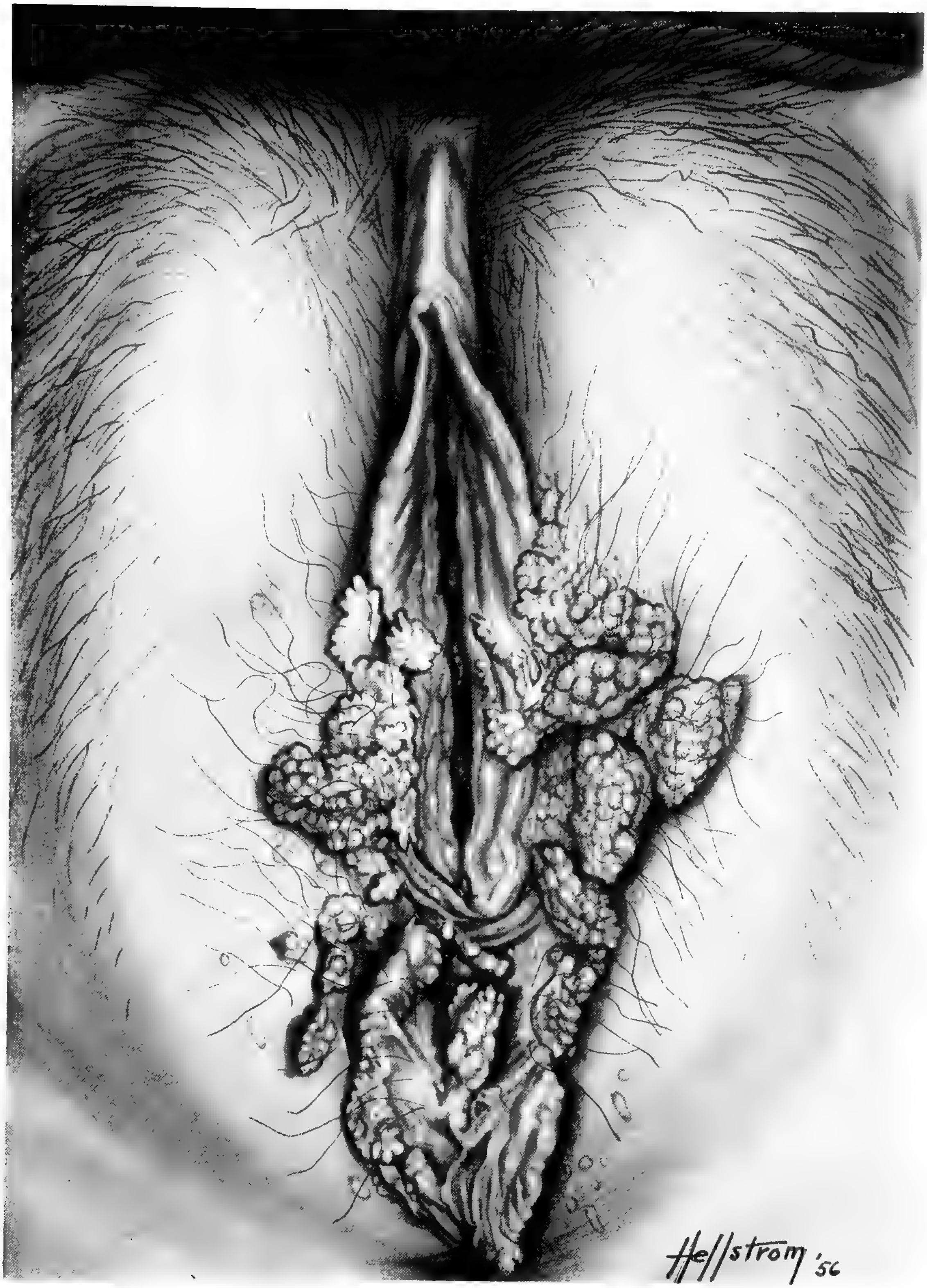


Fig. 20. Condylomata accuminata. Extensive warts about the labia minora, majora, perineum and anus. Caused by a filterable virus. This was treated by trimming away the larger warts and fulguration of the bases.

may simulate carcinoma-in-situ or even early invasive carcinoma. But the gross verrucous appearance and the presence of other warts on the cervix, vaginal wall or vulva, establish its benign character. The rapid growth during pregnancy and the pleomorphic cellularity increases materially the difficulty of diagnosis. In case of doubt radical therapy should be delayed, at least for a short time and further study.

The treatment of condylomata accuminata, and the lesions are usually multiple, includes the application of podophylin and fulguration. Surface lesions, if typical, do not need biopsy. When vaginal lesions are associated with the external warts they may not need biopsy. But lesions of the cervix should have a portion taken for study, because of the extreme importance and frequency of carcinoma of the cervix. When external lesions are not numerous, the local application of podophylin, in concentrations of ten to fifty per cent in alcohol, mineral oil or glycerine, once or twice weekly on three or four occasions, causes rapid disappearance of the warts. It is important that the podophylin be applied only to the warts themselves; if allowed to spread over the vulva, severe pain, swelling and generalized vulvitis may require hospitalization. If allowed to dry on the individual wart (the alcoholic solution dries quickly), the results are highly beneficial. When the warts are widespread and large, treatment by excision and fulguration under pentothal anesthesia is preferable. The larger warts may be snipped with scissors, after which the base of every one is carefully and thoroughly fulgurated with the needle point. This requires minute inspection of the entire vulva, the anus with its tags and hemorrhoids, and also the vaginal wall and cervix. If any warts are

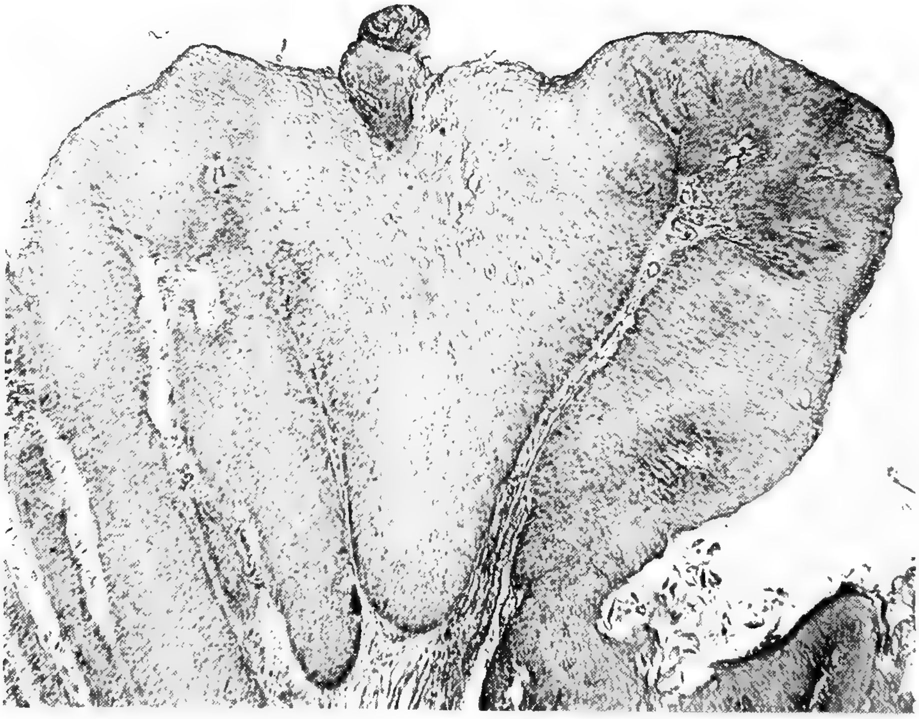


Fig. 21. Condyloma accuminatum of the vulva. This warty growth shows extraordinary proliferation of the squamous epithelium, much thicker than in any other situation. The rete pegs are quite elongated in the papillary arrangement. In some of the warty growths the epithelial cells grow so rapidly that numerous mitoses may be present, and one may suspect malignancy. Rarely is this true, although on extra-ordinary occasion malignant changes are associated with warts of the vulva.

overlooked, recurrence is to be expected. Small, undetected, or recurrent warts may be treated subsequently in the office by local application of podophylin.

SUMMARY OF DIAGNOSIS OF VENEREAL DISEASES

The diagnosis of the ulcerative lesions of the vulva necessitates careful use of a battery of tests. These include (1) dark-field examination for Treponema pallida, (2) serologic tests for syphilis, (3) smears stained with Gram stain for Ducrey's bacillus, (4) intradermal test with Ducrey antigen, (5) scrapings from the ulcer stained with Wright's or Giemsa's stains for Donovan bodies, (6) intradermal Frei test for lymphogranuloma venereum, (7) smears stained with Gram's stain for Vincent's bacillus and spirillum, and finally (8) biopsy to exclude the possibility of tuberculosis and, more particularly, malignancy. Carcinoma is prone to develop in chronic venereal ulcerations, and great care is necessary to rule out this important disease. Often more than one venereal disease may be present, and carcinoma may be an important complication.

NON-VENEREAL INFECTIONS OF THE VULVA

Acute Ulcer of Lipschutz
(Ulcus Acutum Vulvae)

A round or oval superficial and painful ulcer of the vulva, at times multiple, may occur any age, and may be associated with systemic febrile diseases. Smears from the ulcer show the large long black *bacillus crassus,* considered identical with the bacillus of Doderlein. Bacteremia has been reported with this condition. Ordinarily the lesion is quite uncomfortable but heals with cleanliness and local antiseptics. More should be known of the bacteriology of the "acute ulcer."

Monilial Vulvitis (Candidiasis)

The diffusely reddened, slightly edematous vulva, with perhaps white flecks of "cottage cheese discharge," or with minute red raised areas, associated with severe itching and burning, with pain from flow of urine over the surface, often is caused by *monilia* or *candida albicans.* Examination, microscopically, of flecks of the discharge, of scrapings of the vulva, or of secretions of the vagina in saline, may confirm the clinical opinion by revealing the presence of mycelia. These appear as fine translucent branches with minute buds, or, as piled up large masses of mycelia or "brush." The fungus may be made more obvious by darkening the mycelia after application of a drop of ten per cent potassium hydroxide under the cover slip preparation. The vagina usually is involved, if there is vulvitis. The walls may be reddened, or pale and almost normal, with dry discharge of "cottage cheese" type, or watery discharge with or without "cottage cheese" flecks. The urine always should be checked for sugar, as diabetes either increases glycogen in the secretions or causes a deposit of sugar on the vulva from urine, producing optimal conditions for growth of the fungus. If sugar is present in the urine, cure is unlikely without control of the diabetes.

Various methods of treatment are available. Local application of gentian violet, in one to five per cent aqueous solution, repeated daily or twice weekly, formerly was the treatment of choice. The annoyance of the persistent stain, and sometimes unsatisfactory results, have made physicians welcome the use of propionic acid preparations (as Propion-gel), and subsequently phenyl mercuric acetate (Nylmerate jelly, used intravaginally and externally), and more recently intravaginal nystatin, an antibiotic fungicide (Mycostatin). Further discussion follows under Fungus Vaginitis.

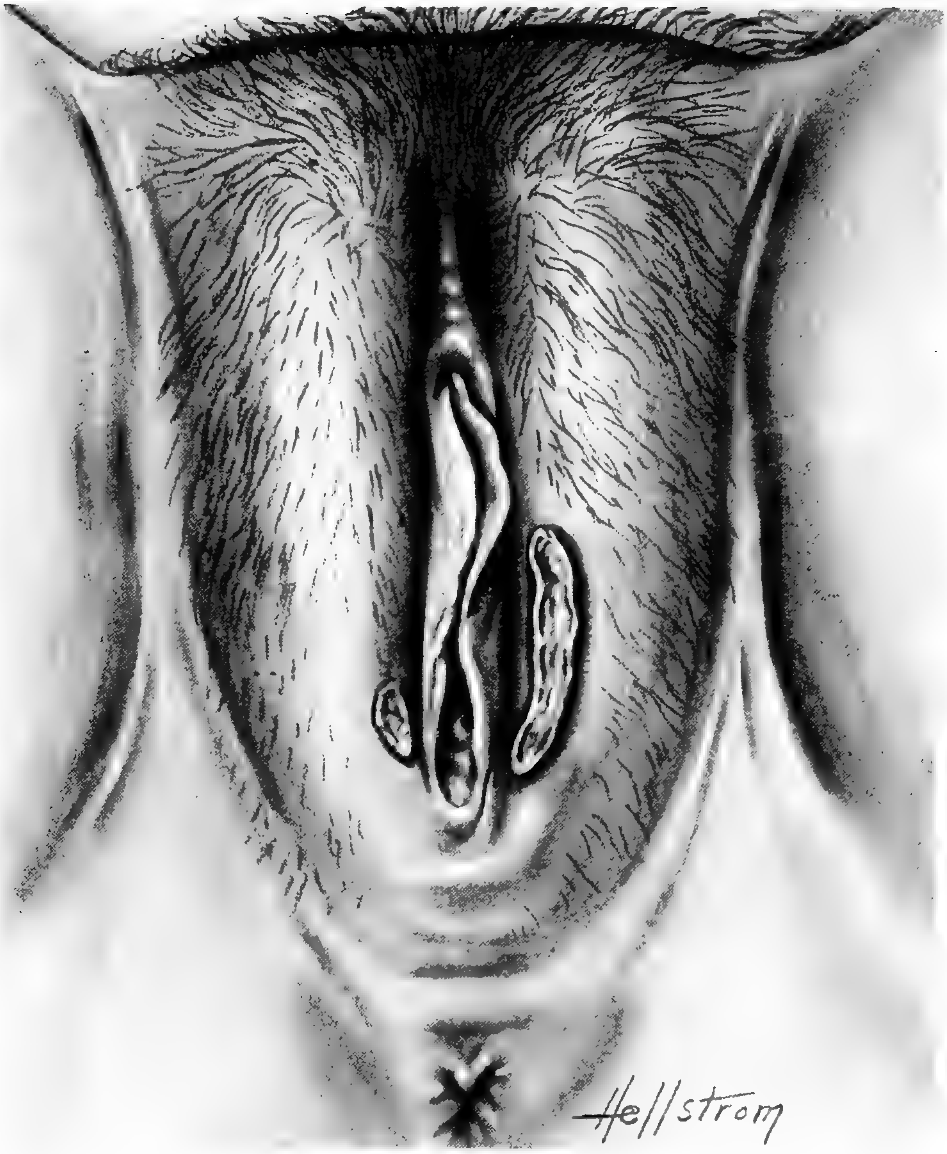


Fig. 22. Ulcus acutum vulvae of Lipschutz. These superficial ulcers occurred during a febrile disease; smears showed B. crassus.

Vulvitis, Trichomonal

Trichomonas vaginalis infections begin in the vagina, extend to the vestibule, urethral ducts, Bartholin's glands and less frequently to the vulva. Itching of the vulva is a common complaint in patients with trichomonas vaginalis vaginitis, though the vulva may appear normal. Occasionally the vulva is moderately or severely reddened, is edematous, and has associated itching and burning discomfort. Diagnosis is made from study of the fresh preparation of the vaginal secretions with demonstration of the motile trichomonas vaginalis. The vulvitis disappears rapidly after specific treatment of the vaginitis.

Follicular Vulvitis

A diffuse red papular or pustular vulvitis occurs occasionally, and is due to a staphylococcal infection of the sebaceous and sweat glands. Cleanliness, local heat, drying, and, if necessary, local antibiotic ointment or parenteral antibiotics, usually result in rapid improvement.

Furuncle

Infection in individual sebaceous glands and hair follicles is quite frequent, and usually also is caused by the staphylococcus. After hot sitz baths, or hot packs, they either open and drain, or are absorbed. Occasional severe infections require incision and drainage, and antibiotic therapy. Recurrence or recrudescence of small furnucles is extremely common, probably because of secretions, moisture, body heat, hair, menstrual absorbent pads, and clothing.

Intertrigo

Chafing and maceration, which occur in the folds of the thighs and buttock, are known as intertrigo. A similar reaction occurs under large, pendulous breasts. It occurs commonly in the obese, especially in hot weather. Drying antiseptic powders are of temporary value. Reduction of weight in the obese diminishes friction in these moist, poorly aerated surfaces.

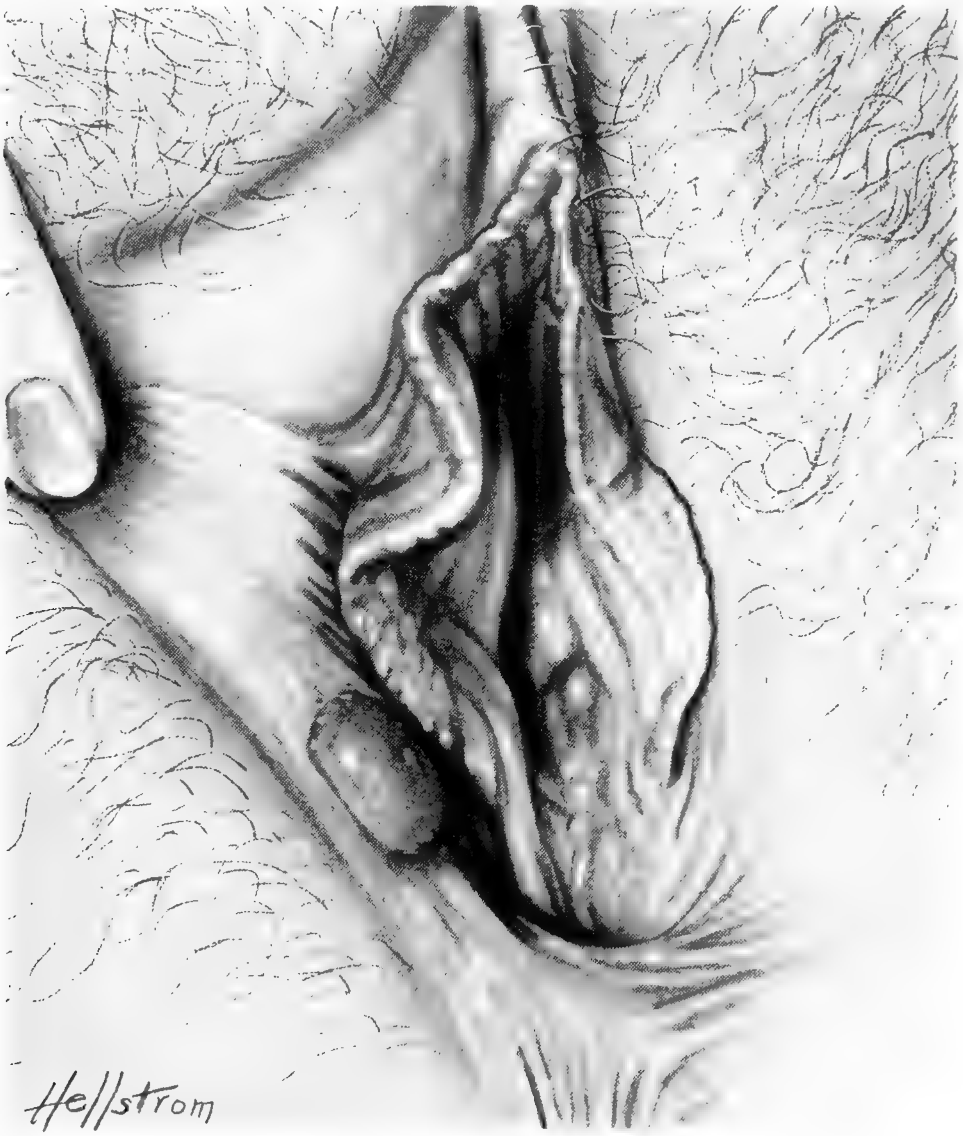


Fig. 23. Sebaceous cyst of vulva. Usually round, raised, yellowish, rubbery, commonly multiple. Unless infection occurs, asymptomatic. Very frequently occurring, evidently becoming malignant extremely rarely.

Tinea Cruris

Epidermophyton inguinale, and less commonly, *Trichophyton puerperium* and *Trichophyton gypseum* produce a clinical picture called tinea cruris or eczema marginatum. Redness, scaling, vesiculation and maceration may extend laterally over the vulva and about the anus. The advancing margin has a well-defined elevated border. This pruritic lesion is aggravated by moisture, heat and friction. The fungus can be seen in scrapings, especially after application of potassium hydroxide under the cover slip. Seborrheic dermatitis and psoriasis are considered in differential diagnosis. Treatment is by application of calamine lotion containing two to four per cent resorcin, or the newer fungistatic agents (Desenex or Sopronol).

Pediculosis Pubis

This annoying parasitic disease of the vulva is caused by the crab louse, transmitted by contact, often during sexual intercourse. There is marked itching followed by scratching and secondary vulvitis. The diagnosis is made by finding the minute brownish-white mobile louse, and by finding the very minute white eggs (known as nits), near the base of the pubic hairs. New medicinals are very effective; a shampoo on one or two occasions is followed by cure.

Scabies

The severe itching of scabies (the "seven year itch") is produced by the itch mite, which burrows under the skin, especially on the fingers. The disease on occasion is more prominent on the vulva; abrasions and irritation result from the severe scratching. Drugs introduced recently have proven effective for rapid cure. These include benzyl benzoate-tyrothricin compounds (Tyroscabe, Sharpe and Dohme) and hexachlorocydohexane (Kwell, Commercial Solvents).

INFREQUENT INFLAMMATORY LESIONS OF THE VULVA

Tuberculosis

Tuberculous ulcers of the vulva were described frequently in earlier times. They may start as a primary infection in the vulva or may extend down gradually from infection in the fallopian tubes, with secondary and diminishing frequency in the endometrium, cervix, vagina and vulva. A round or irregular ulcer, not indurated, which fails to heal used to be the most frequent form. Lupus-like lesions with so-called "apple-jelly nodules," or rarely elephantiasis and chronic hypertrophic vulvitis, also were forms of the disease. The lesion has become exceedingly rare.

Gangrenous Vulvitis, or Noma

Gangrenous vulvitis, or Noma, has been described as a severe ulcerative destructive lesion of the vulva, formerly was seen during the course of infectious diseases of childhood, such as variola, varicella, diphtheria, or scarlet fever. It started as a furuncle and spread rapidly, and the vulva became gangrenous. Extensive thrombosis of veins occurred and the mortality was high. Improved hygiene and general nutrition, vaccinations and the antibiotics probably are responsible for practically eradicating this often fatal complication.

Erysipelas

Erysipelas of the vulva, a streptococcal infection of the skin and subcutaneous tissues, occurs as an acute infection with raised, sharply defined border. The patient develops chills, fever, and toxicity. Antibiotics ordinarily control this infection.

Cellulitis

Cellulitis of the vulva is a deeper infection of the vulva, more localized, spreading less rapidly, usually secondary to more superficial infection, as the furuncles. Antibiotics, local heat and rest are effective. Incision and drainage may be necessary when suppuration develops.

Diphtheritic Vulvitis

Diphtheritic vulvitis, while exceedingly rare now, formerly was very important. It may or may not be associated with pharyngeal diphtheria, and occurs most commonly in children. The vagina also is involved. A necrotic greyish-white adherent membrane, associated with constitutional symptoms of fever and malaise, indicate a need for examination of smears and cultures for the Klebs-Loeffler organism. Immunization is preventive, antitoxin is curative. Severe vaginal wall involvement may lead to scarring with extensive stenosis.

NEUROGENIC DISEASES OF THE VULVA

Pruritis Vulvae

Pruritis vulvae, and pruritis ani, or a combination of the two really are symptoms of itching. When either of these terms is used as a diagnosis, one assumes that all other diseases of bacterial, viral, fungal, protozoal, parasitic or trophic origin have been eliminated as a cause. The more carefully these factors are explored, the more frequently such etiologic agents are found. Discharges due to cervicitis and vaginitis are quite important, and care of these often relieves the pruritis. One complicating agent may be a fungus. While this latter is a definite factor in many instances, cultures of the vulva and vagina reveal candida more often in the absence of any clinical disease. Allergies due to medicinal agents, and friction due to menstrual absorbent pad, may be causes. Pruritis vulvae is commonly related to nervous tension, anxiety or psychosis. The vulva may appear normal. If severe itching has been present, excoriations are likely to be present, and secondary vulvitis may be severe. With chronic itching, the skin over the prominent portion of the labia majora becomes thick and white. This is called lichenfication, and differs from leukoplakia mainly in its distribution. In the latter, the thick white appearance is always more marked around the inner surfaces of the labia majora, and over the labia minora, prepuce and clitoris.

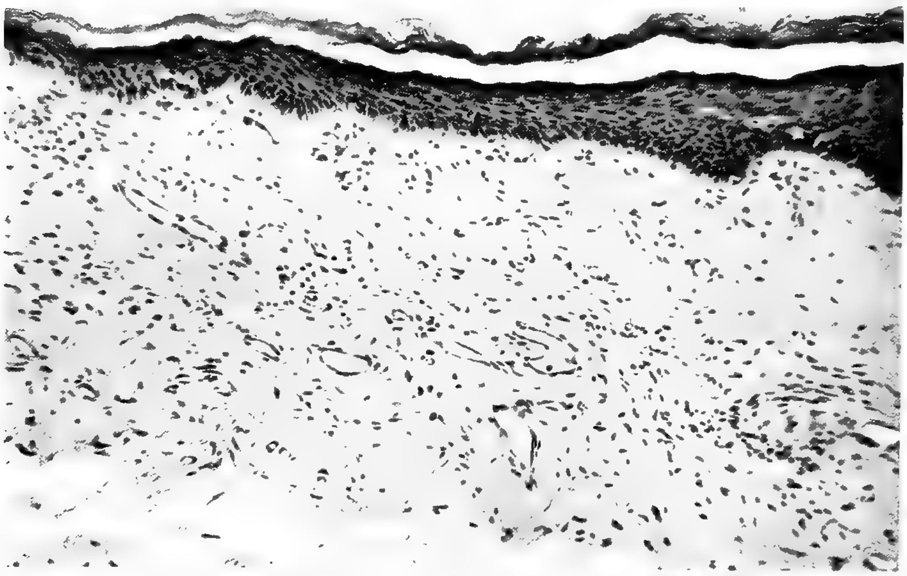
Treatment includes antihistamine ointments, soothing lotions, local anesthetic creams, x-ray therapy in skin doses, mild sedation, reassurance and occasionally psychotherapy. Rarely absolute alcohol is injected beneath the corium, one-tenth cubic centimeter at one centimeter intervals, according to the method of Stone (beware of slough of skin); anesthetic agents in oil may be deposited beneath the skin outlining the vulva (beware of sensitivity); and extremely rarely, the undercutting operation of Mering, breaking the continuity of the nerves entering the deep fascia is necessary, and very helpful. In this operation the entire vulva is mobilized by blunt dissection, after two incisions are made over the prominent portion of each labium major, extending down to the deep fascia. Often the patient is relieved by various simple measures temporarily, but recurrence is frequent.

TROPHIC DISEASES

Kraurosis Vulvae

Kraurosis vulvae literally means thinning of the vulva. After the menopause, the ovaries may cease production of estrogens abruptly, or may gradually decrease their function over a period of months or years. Estrogens may persist for some time from another source, apparently the adrenal cortex. A study of vaginal smears and the thickness of the vagina indicates that estrogen secretion

Fig. 24. Atrophy of vulva or kraurosis of vulva. The surface squamous epithelium is unusually thin in the left side of the photograph. Only four or five layers of squamous epithelial cells are present where normally there may be present fifteen or twenty layers. The cells themselves have a smaller amount of cytoplasm. A slight chronic inflammatory reaction is present beneath the surface epithelium, probably a reaction of irritation from pruritus.



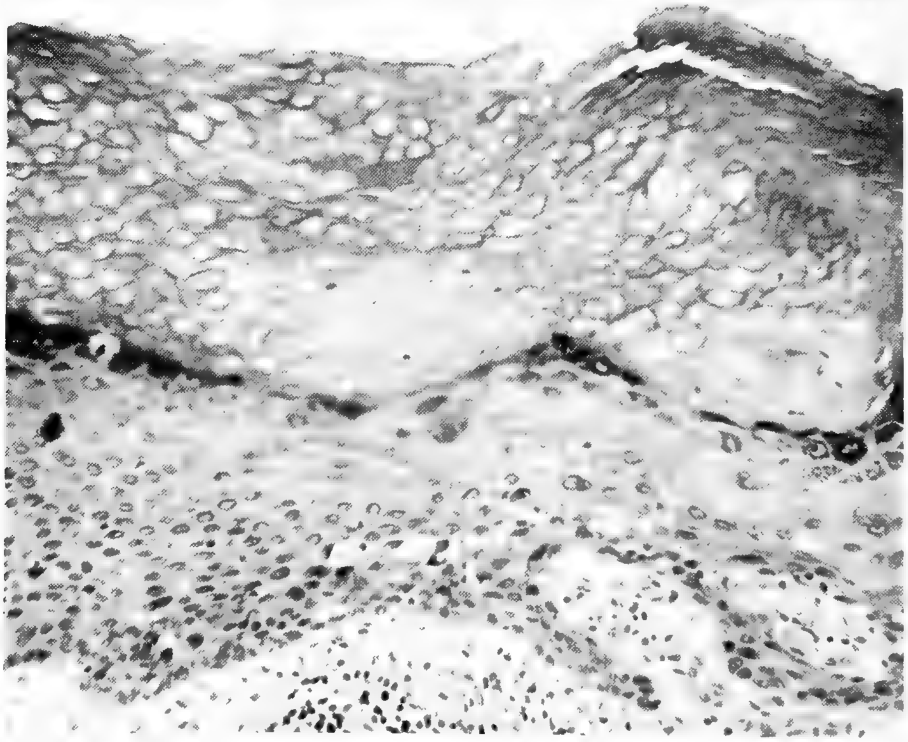


Fig. 25. Leucoplakia of the vulva, characterized by marked thickening of the epithelium, prominent eleiden layer and intense horny layer on the surface. The rete pegs are more prominent than normal, and there is some basal cell hyperplasia.

is withdrawn abruptly in approximately one-half of women, and that eventually nearly all show complete absence of estrogen. The vulvar skin and its fat pads are more sensitive to estrogens than the skin and panniculus of other parts of the body. This explains the postmenopausal atrophy of the external genitalia. The labia majora become much smaller, the skin thinner, the labia minora recede and may disappear, and the mucocutaneous junction around the vestibule becomes very thin, pale, delicate, and sensitive. These atrophic changes may be prevented or retarded by the ingestion of estrogens or the application of estrogen creams. Ordinarily, normal atrophy is associated only with dyspareunia, due to the thin, tender vulva and vagina, and constriction of the orifice. The tenderness from this atrophy is the chief cause of the loss of interest in sex relations, which often occurs after the menopause. If the discomfort from the atrophy is prevented, interest and pleasure in sexual intercourse may be prolonged as long as the woman chooses or has the stamina and the physical energy required for sexual activity.

In rare instances the vulva develops severe shrinkage and extraordinary thinning of the skin and mucocutaneous border. These changes may be associated with burning discomfort, severe dyspareunia and marked pruritis. This is an exaggeration of the atrophy which occurs normally, but there is no explanation why it should advance to such a marked degree. Histologic examination reveals thinning and atrophy of the squamous epithelium with no abnormal nuclear changes. One would think the process could be reversed by substitutional estrogenic therapy. The use of estrogen creams locally, estrogen orally daily or twice weekly, or of estrogens parenterally (and parenteral administration never seems better than oral administration) are surprisingly disappointing in improving kraurosis. Symptoms generally are improved to some degree, especially by the estrogen creams, but reversion to normal does not occur. A largely irreversible atrophy has occurred. Soothing lotions, antihistaminic creams, warm tub soaks, and mild sedation, accompanied by healing of the secondary infection that may follow scratching, give temporary relief. Like so many skin conditions, there may be no permanent cure, and constant care and special attention may be necessary. Acute vulvitis may occur with kraurosis vulvae and is probably secondary to scratching. It requires hot packs, local antiseptics, and antibiotics.

Leukoplakia Vulvae

Leukoplakia literally means white plaque, and connotes discrete thick white areas with sharp borders outlining the abnormal area. However, the lesion is not quite so well defined. It includes a rather irregular blend of diffuse white thickening of the *inner surfaces* of the labia majora and the minora, and the clitoris and prepuce. The thickening is most evident medially at the mucocutaneous border, extending onto the inner surfaces of the labia majora. This thick, parchment-like change in the skin extends laterally on the majora, commonly in a butterfly manner to the sides of the anus, and occasionally surrounds the anus severely. Constriction of the vagina and anus occurs in the extreme cases. The majority of cases occur after the menopause, but at times leukoplakia may occur before the menopause. A few cases have been reported in children.

Leukoplakia may or may not be associated with kraurosis. Probably in half the cases an obvious abnormal thinning of the vulvar skin is present surrounding the medial leukoplakia, or extending intermittently between the white areas up to the vaginal orifice. In perhaps another half the surrounding skin shows no more than normal atrophy or may seem essentially normal. The term kraurosis with leukoplakia, or the reverse, is descriptive in many cases. These two terms have been used interchangeably in the literature, with resultant confusion. Another term, leukoplakic vulvitis, would seem to indicate that inflammation is of primary importance. The inflammation probably is secondary to scratching.

The labia minora tend to disappear in the thick leathery skin, and the prepuce is prone to the same leukoplakic change. The clitoris becomes thickened over its surface, and may retract and disappear under the parchment-like skin. In early cases, only the prepuce may show leukoplakia. This small area is also prone to the development of carcinoma.

The etiology of leukoplakia of the vulva is unknown. Estrogen deficiency has been implicated, but almost all women develop anestrogenemia eventually, as judged by the vaginal smear. Deficiency of vitamin A may be an important factor in this change. Gastric achlorhydria and secondary anemia have been thought to have a causal relationship, but these deficiencies are of doubtful importance.

Histologically in a simple case, the skin is markedly thickened, with some hyperplasia of the granular layer, much proliferation of the squamous or prickle-cell layer (acanthosis) and a thick hyalinized layer on the surface (parakeratosis). Many years ago. Hinselmann described three degrees of leukoplakia, based on the amount of hyperplasia and atypia in the basal cell layer. A partial extension of the basal cell layer into the spinal cell layer was called rho I; a complete extension of the basal cells up to the surface, with few nuclear changes, was called rho II; marked cellular changes, consisting of abnormal mitoses, giant nuclei, intracellular edema, and intranuclear edema, was called rho III. This microscopic classification is

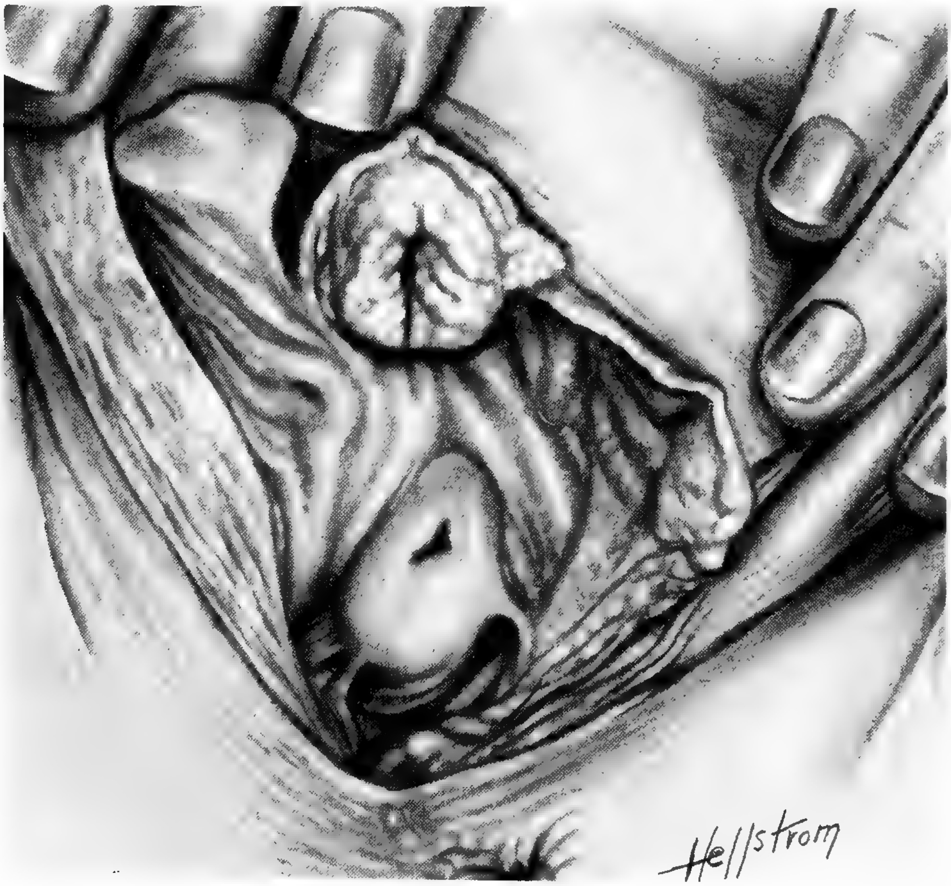


Fig. 26. Leukoplakia of clitoris. Only this area and prepuce is involved. Age 50 years, postmenopausal. Marked improvement after treatment with vitamin A, estrogen and cortisone cream.

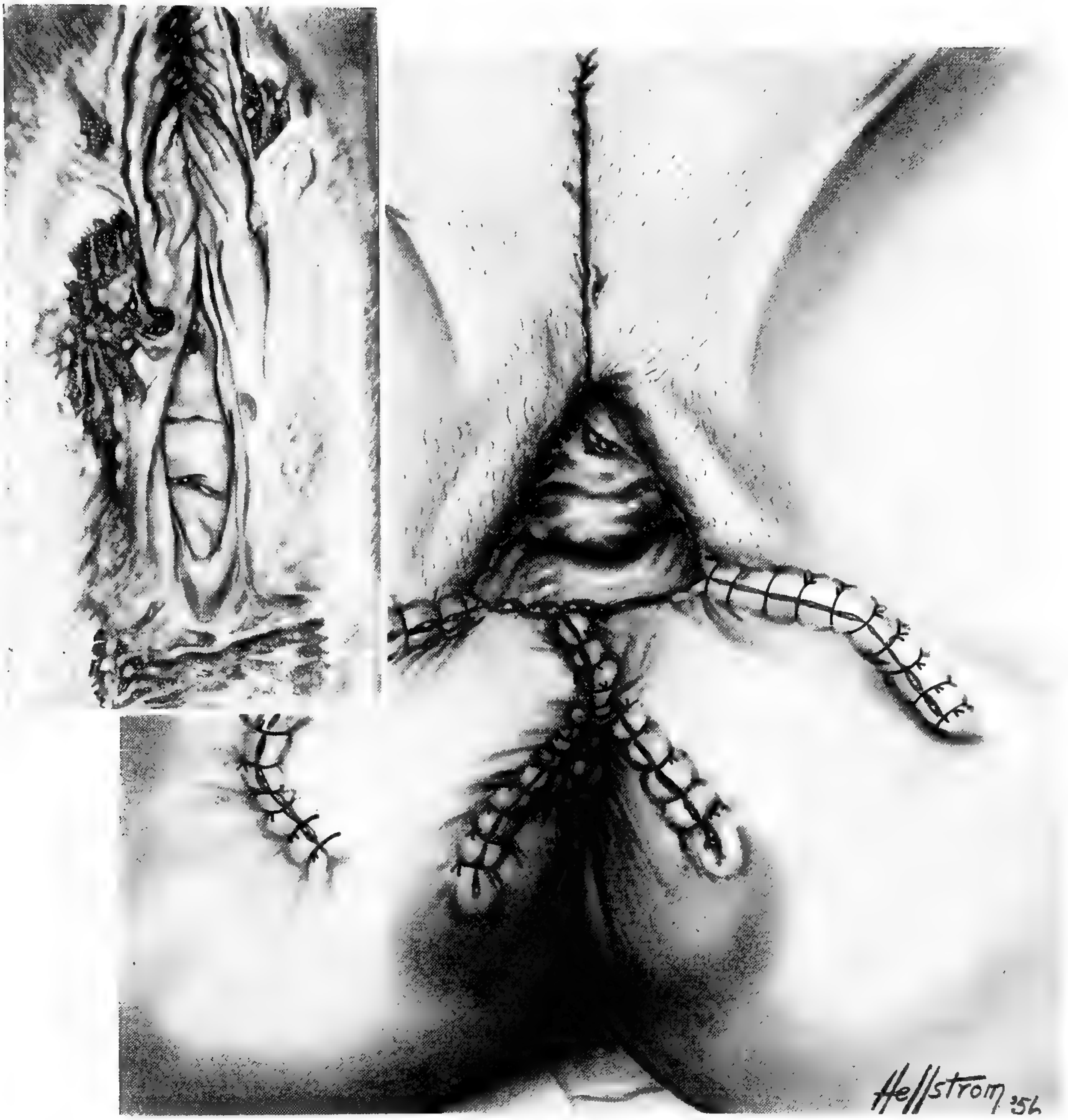


Fig. 27. Squamous cell carcinoma of vulva, arising in leucoplakia, age 68 years. Multicentric origin, mid-labia on right and upper left. Marked pruritis and ulcerations, treated by ointments for past year. Note wide excision, especially in perineal area. Flaps from buttock are used in closure. Subcuticular chromic sutures above, and interrupted silk was used posteriorly. One week later had radical inguinal, femoral, and external iliac lymph node dissection. All may be performed in one stage, if patient is in reasonable condition.

particularly applicable to the cervix uteri, more so than the vulva, and rho III is a form of carcinoma-in-situ. When these changes occur in the vulvar skin, with the gross appearance of thick white leukoplakia, some degree of malignant potentiality should be anticipated. But invasive squamous cell carcinoma may develop from the basal cell hyperplasia. Leukoplakia of the vulva is not uncommon, but carcinoma of the vulva is rare. It is evident that only a small percentage of cases of leukoplakia change into squamous cell carcinoma, but it is impossible to determine which ones will do so. Minute roughened areas on otherwise smooth leukoplakia are ominous and should be biopsied. Ulcers, minute or large, are cause for concern and should be examined histologically.

Leukoplakia of the vulva should be treated therapeutically or surgically. As a rule, the patient seeks relief for intense pruritis. If the lesion is not severe or suspicious of malignancy, medical treatment consists of vitamin A 300,000 units daily, antihistaminic ointments, other antipruritics such as Burrow's solution (which is also available in Acid Mantle cream), and estrogen cream to the vulva and vagina. Mild sedation with phenobarbital one-fourth grain, three times daily, or tranquillizers, may alleviate the itching to some degree. Even marked degrees of leukoplakia of the vulva may be improved with this regime. But one must be so very careful not to procrastinate with early malignant changes. When there is any doubt as to coexistence of carcinoma, biopsy is essential. X-ray therapy is inadvisable, because radiodermatitis may follow, and this may be even more cancerogenic than leukoplakia.

Simple vulvectomy is indicated for marked leukoplakia, especially if there is no visible improvement following a trial of medical therapy. Excision should include most of the labia majora, the labia minora to the uninvolved vestibule, and the clitoris and prepuce. The excision should extend to the sides of the anus in a butterfly manner if indicated, and the perineal skin between the vagina and rectum must be removed as necessary. The defect to the sides of the anus may be closed more effectively by swinging a flap of skin in from each buttock, as shown in Fig. 27. Subcuticular continuous chromic suture is quite satisfactory for the closure of the upper skin, also the skin and vagina, but interrupted suture of silk may be better near the anus. The resultant deformity is somewhat disturbing but is well compensated by the relief of the itching. Sexual relations may be normal.

Leukoplakia tends to recur along the lines of excision, sometimes to a severe degree. Medical therapy may bring improvement, but in occasional cases, re-excision is necessary.

Lichen Sclerosis et Atrophicus

This white appearance of the vulva, associated with degrees of atrophy, may occur before puberty, during menstrual life, and more frequently after the menopause. When the disease occurs before puberty, the inner surfaces of the labia minora become white, faintly thickened, and the child complains of pruritis. Usually it improves or disappears after the onset of menstruation. In older women near or after the menopause there is much atrophy of the labia minora, prepuce and clitoris, and the white, slightly glistening skin surrounds the vagina, and particularly extends about the anus (to a degree more characteristic than leukoplakia). Similar lesions of the skin may occur on the lower abdomen, back of the neck, wrists and ankles. Atrophy is prominent, and though the white appearance suggests leukoplakia, the skin does seem thin and fragile. "Cigarette-paper wrinkling" has been used as a descriptive term. Itching is a prominent symptom, and may cause excoriations and degrees of vulvitis. This condition probably has been considered kraurosis vulvae in many instances; in fact, the so-called kraurosis of severe degree often represents lichen sclerosis. Twenty-five years ago, many prominent dermatologists considered this an atrophic form of leukoplakia.

The microscopic pathology is characteristic. The stratified squamous epithelium may be thinner than normal, six to ten layers thick, with no increased cornification. In some areas there may be acanthosis. Mitoses are infre-

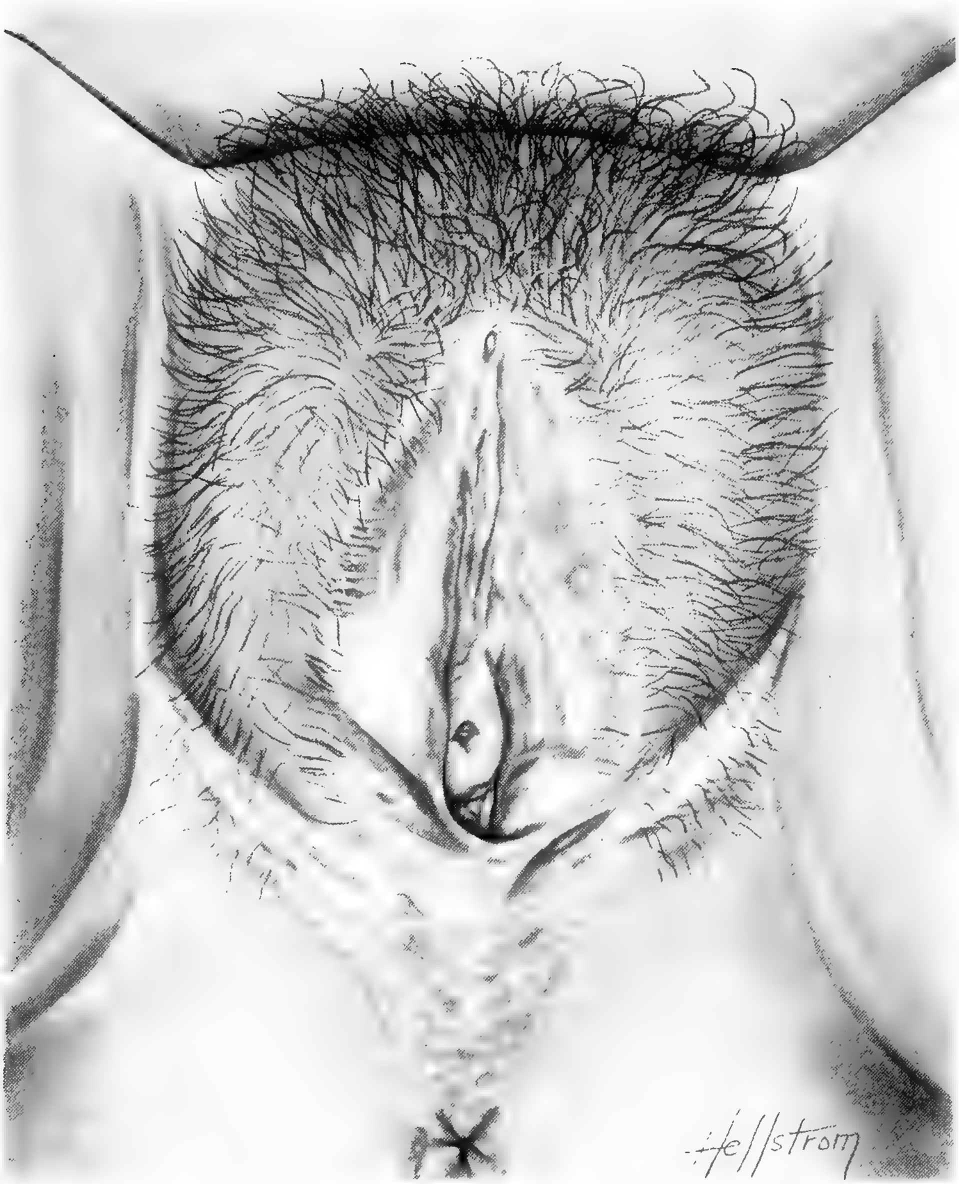


Fig. 28. Lichen sclerosis et atrophicus. Note the disappearance of labia minora, the thin appearing, and yet white skin with "cigarette-paper" wrinkling. The involvement characteristically extends about the perineum and the anus, more than does true leucoplakia. Also there is extension into the genito-crural folds. This patient was menstruating regularly and had normal estrogenic smears. Most often this occurs post-menopausally.

quent, and nuclear hyperchromatism is not a marked feature. Beneath the thin layer of squamous epithelium is a prominent hyaline layer in the corium, often several times thicker than the squamous epithelium. The nature of this change in the corium is unknown. Inflammation is not characteristic, but may follow scratching from pruritis.

Small areas of similar lesions may be found on the wrist, ankle, lower abdomen and back of the neck. Thus, this disease is more of a generalized skin disease than true leukoplakia, and may be similar or related to lichen planus.

In the prepubescent child, estrogen cream, antihistamine lotion, and cortisone ointments

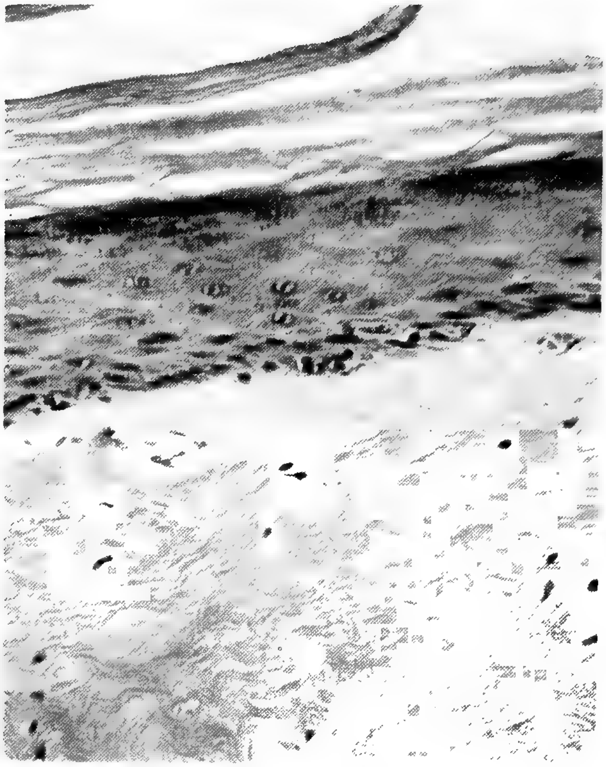


Fig. 29. High power view of lichen sclerosis et atrophicus. The epithelial cells show no hyperactivity of growth effect or irregularity of nuclei. The sub-epithelial hyalinization is characteristic.

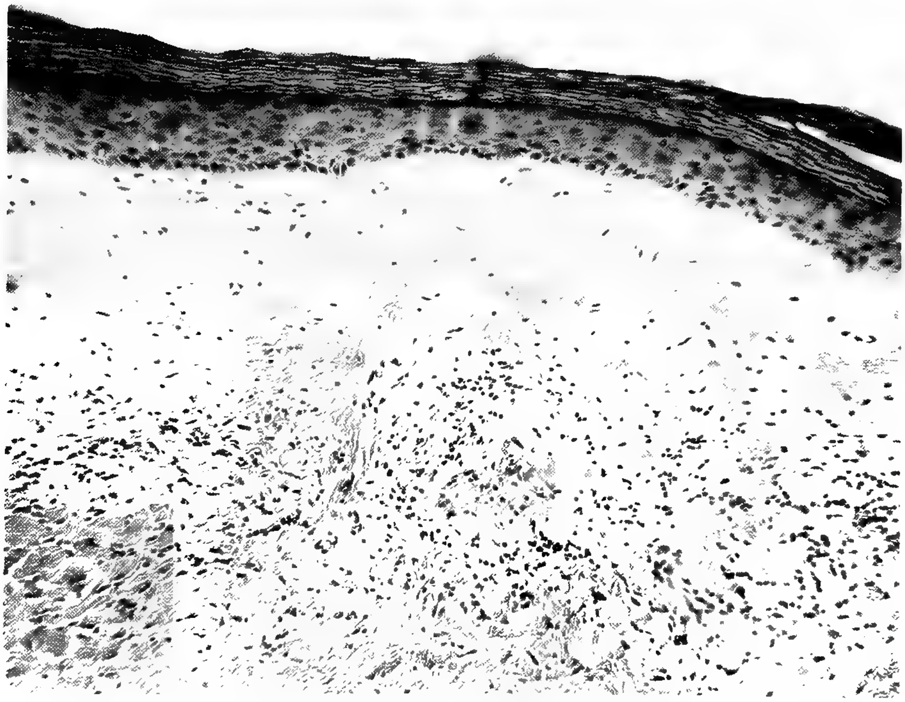


Fig. 30. Lichen sclerosis et atrophicus of the vulva. The squamous epithelium here is not thickened, in fact is slightly thinner than normal, but has an increased parakeratosis. Sometimes the epithelium is quite thickened in this condition. More characteristic is the sub-epithelial hyalinization in the corium. Beneath this is shown a slight chronic inflammatory reaction.

may give temporary improvement. One hopes that puberty will cure this condition. In older women, similar treatment is indicated. Remission of symptoms and spontaneous improvement may occur. With almost any treatment, improvement may follow, but recurrence of symptoms and increased severity of the atrophic changes commonly may be expected. Burrow's solution, and its preparation in cream (Acid Mantle), may give much improvement. At times vulvectomy may be necessary to relieve the itching.

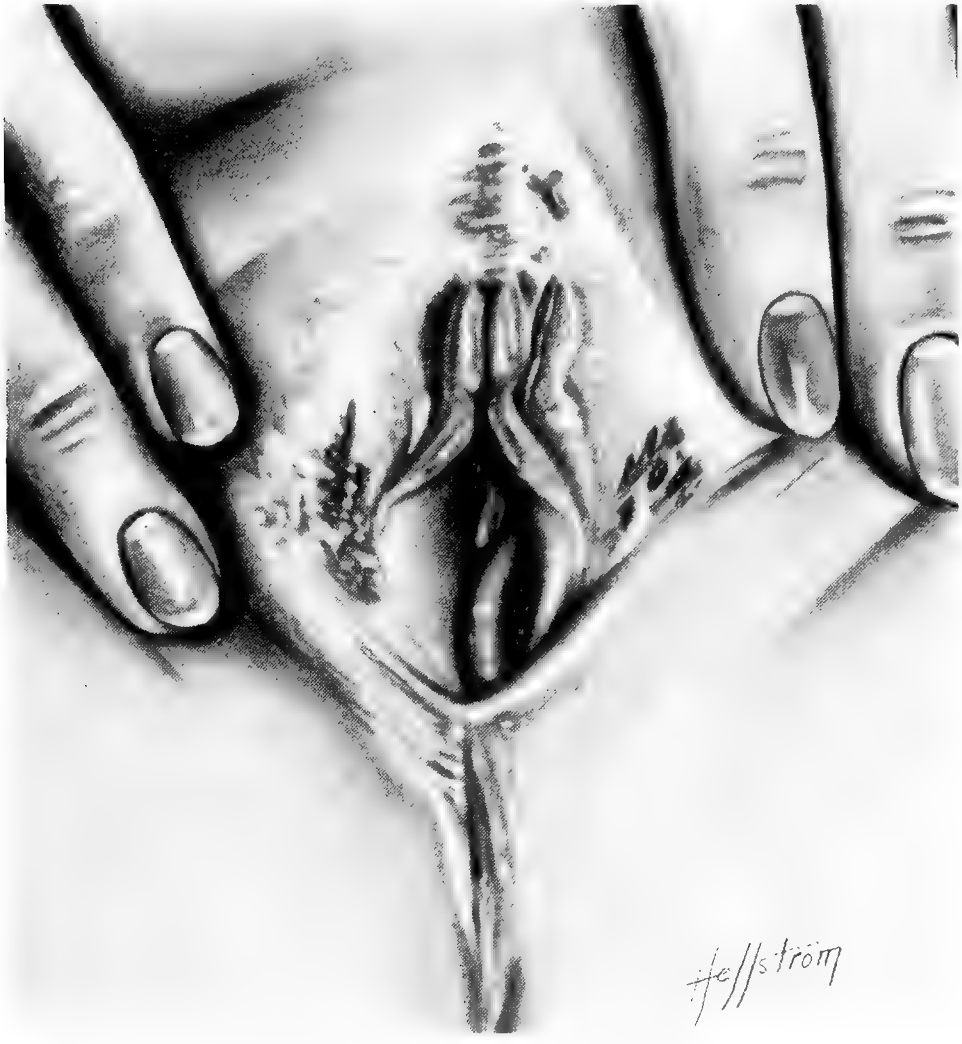


Fig. 31. Lichen sclerosis et atrophicus in a child, age six years. A moderately thickened, white change, irregular and extending along the perineum to the anus. The deep excorations are due to marked pruritis. Improved with estrogen cream and Burrow's solution cream (Acid Mantle). Usually, this lesion is said to improve or disappear with puberty.

OTHER PRECANCEROUS LESIONS

Carcinoma-in-Situ, Bowen's Disease, Paget's Disease, and Basal Cell Epithelioma.

Carcinoma-in-situ

Carcinoma-in-situ is a rare lesion, round or oval in shape, one or two centimeters across, greyish and granular. It causes intense itching and does not respond to medicinal therapy. It is not associated with leukoplakia of the vulva (although its microscopic characteristics are similar to those of rho III leukoplakia). Par-

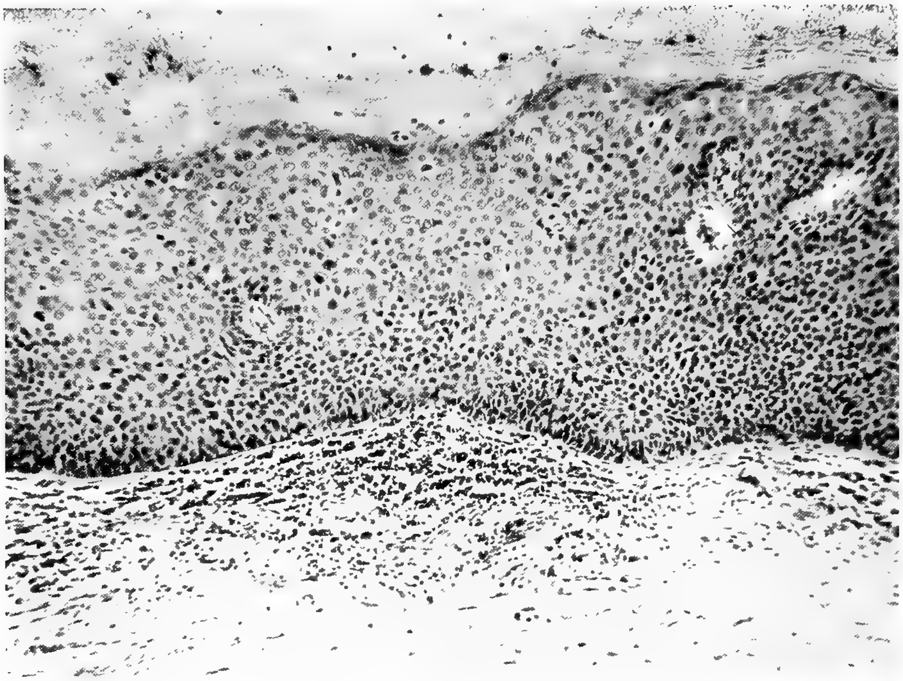


Fig. 32. Carcinoma-in-situ of the vulva. A localized area of non-invasive carcinoma. The epithelium is thicker than normal, probably twice normal thickness. The basal cells have grown all the way to the top of the epithelial layer. Remarkable changes in the nuclei in size and shape, with intra-cellular edema, intra-nuclear edema, and giant nuclei, also are associated with frequent and abnormal mitoses. There is no invasion. A moderate chronic inflammation is present beneath this pruritic, isolated, singular, grayish lesion of the vulva. It progresses into invasive cancer.

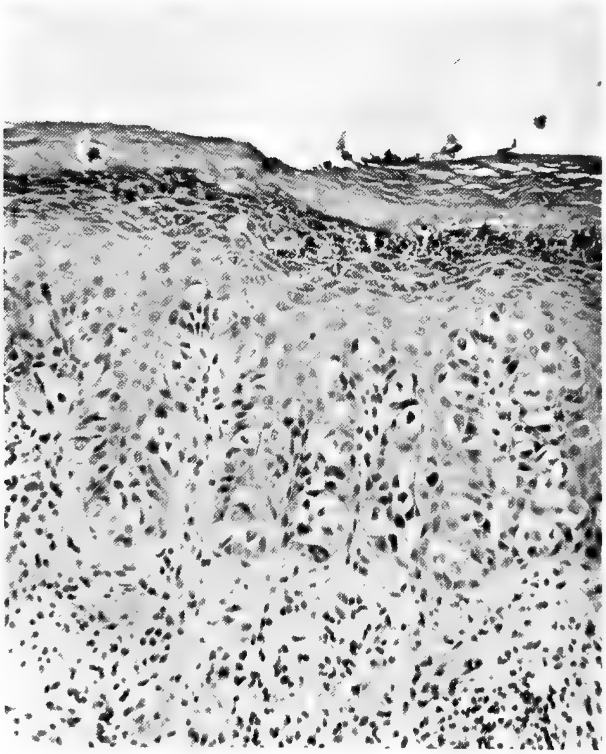


Fig. 33. Paget's disease of the vulva. The squamous epithelium here is thicker than normal, has dipping down of the rete pegs, and increased parakeratosis, but more outstanding in this photograph are the Paget cells growing in the squamous epithelium. These large cells, with vacuolated cytoplasm and enlarged nuclei with varying degrees of irregularity, are characteristic of this disease, which occurs more often in the nipple and areola of the breast. This lesion will progress into an invasive cancer of the vulva.

ticularly, it may occur during menstrual life. Apparently it is an incipient stage of invasive cancer. Simple vulvectomy suffices, if examination of multiple sections shows it is not a well-established carcinoma.

Bowen's disease

This is an intriguing entity, described by Bowen in 1912, as mulberry-colored, slightly granular, pruritic lesions on the skin. Since then, this disease has been reported in the epithelium of the vulva, cervix, mouth, trachea, esophagus and cornea. Histologically there is extension of the basal cells up into the spinal cell layer, with gradual maturity, but with great variation in the size and shape of the nuclei, normal and abnormal mitotic figures, intracellular edema and intranuclear edema. Apparently this lesion may require as many as fifteen years, before it develops into squamous cell carcinoma, yet is considered a premalignant lesion, and should be treated by local excision.

Paget's disease

Paget's disease of the vulva is another rare lesion, characterized microscopically by the presence of large edematous cells in the epithelial layer of the skin. This lesion grossly presents a sharply demarcated, reddened eczematoid and ulcerated area, which causes tingling, itching and pain. The characteristic Paget cells lie singly or in groups among the non-neoplastic squamous cells. These are large, round, or oval cells with large vesicular nuclei and finely granular or vacuolated cytoplasm. They arise from the epithelium of the apocrine glands and extend secondarily into the squamous epithelium. Infiltrating carcinoma may develop. Treatment is by simple excision in the early stage, and radical vulvectomy for invasive carcinoma.

Basal cell carcinoma

Basal cell carcinoma of the vulva is exceedingly rare and resembles similar lesions on the face. It may ulcerate (rodent ulcer) and rarely metastasizes. Local excision suffices for cure.

TUMORS OF THE VULVA

Carcinoma of the vulva

Carcinoma of the vulva is rare. Yet, it is of great importance when it does occur. Analysis of the histories shows that most patients neglect themselves and use various proprietary salves for the itching ulcers that will not heal. Physicians may not recognize the seriousness of the ulcerations or of the leukoplakia.

Vulvar cancer occurs more between the ages of fifty-five and seventy years of age, with the highest incidence at about the sixtieth year. Most of the cases follow leukoplakia; a few follow carcinoma-in-situ, Bowen's disease, or Paget's disease. Some develop in the venereal granulomas of chancroid, granuloma inguinale, and lymphogranuloma venereum. Diagnosis may be aided by cytologic cell studies of smears from the lesions, but definitive diagnosis depends upon biopsy. A mild or moderate degree of leukoplakia does not require biopsy, or vulvectomy, but calls for continual observation. Small, roughened, granular areas or ulcerated areas should be examined histologically without delay.

The microscopic characteristics include the usual changes of squamous cell carcinoma, with invasion from the basal cell layer into the corium and subcutaneous fat. Epithelial pearls are the rule. The lesion is relatively slowly growing, metastasizes not too quickly, and is insensitive to irradiation therapy. This does not necessarily hold in all cases, because sometimes even advanced carcinomas benefit temporarily after irradiation therapy.

For this reason of radio-insensitivity and because of the accessibility of the carcinoma, vulvectomy is indicated. A generous portion of the skin is removed, especially if the growth is large. Wide excision may require skin-grafting. Regional lymph node excision also is indicated. The inguinal, femoral, and external iliac nodes are removed *en bloc.*

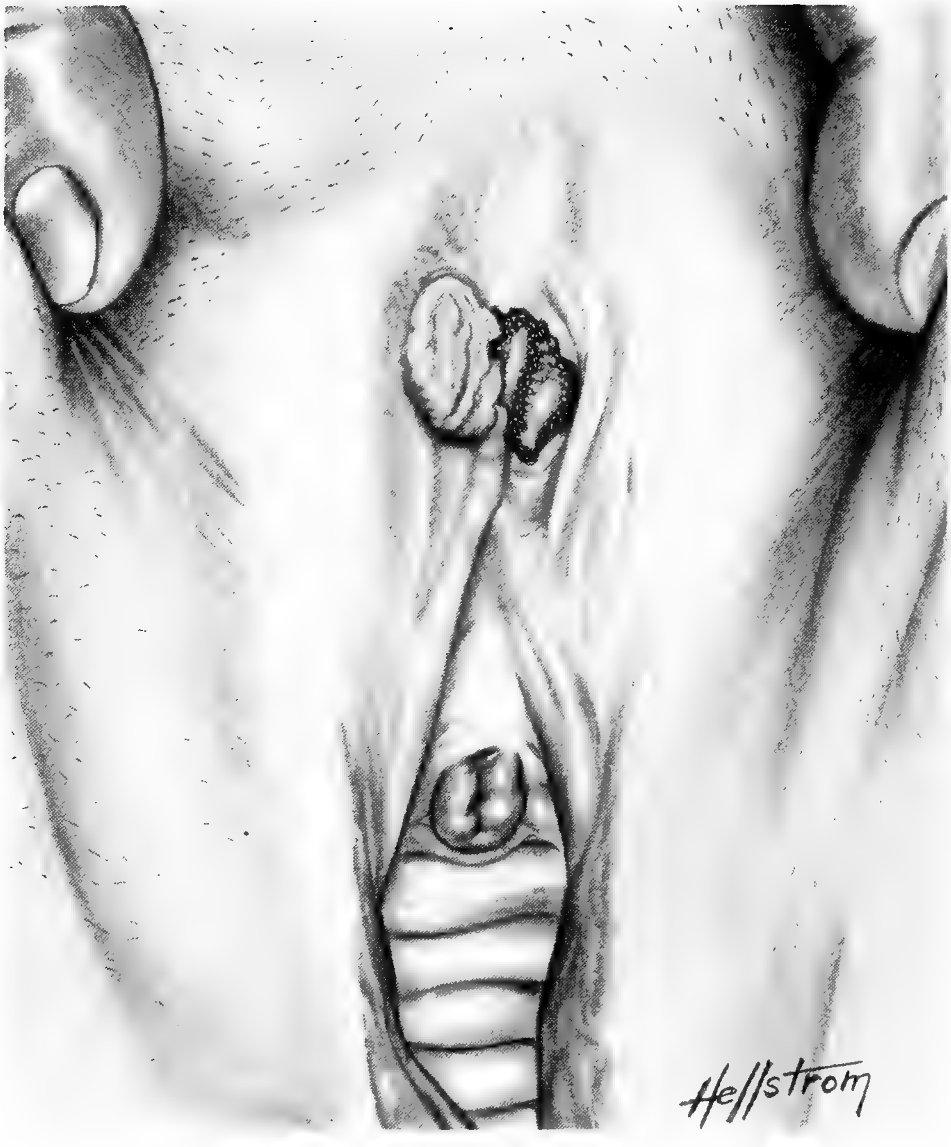


Fig. 34. Carcinoma of clitoris. Ulcerative destruction has displaced the indurated prepuce to the right. The inner surfaces of the labia majora show the white thickening of leukoplakia and the minora show atrophy, more on her left. A moderate prolapse of the urethral mucosa is incidental.

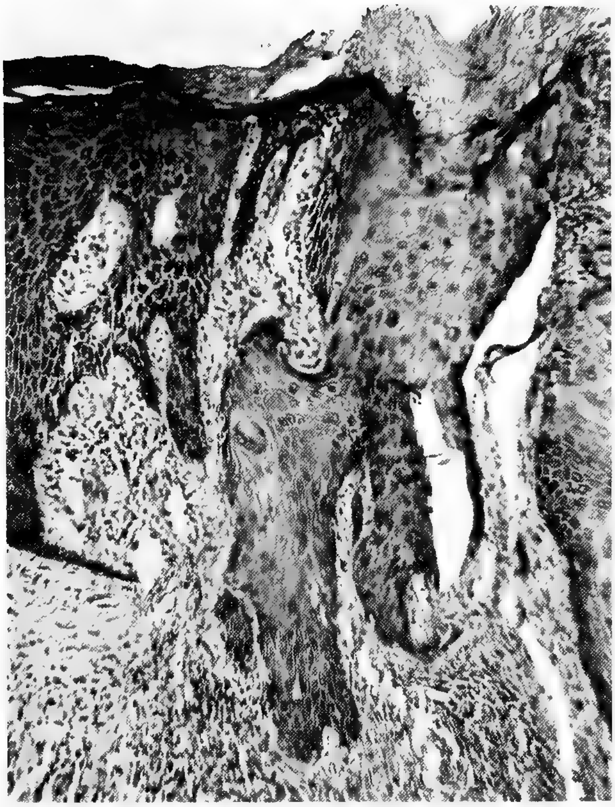


Fig. 35. Relatively early squamous cell carcinoma of the vulva. On the left is shown a degree of leukoplakia. The epithelium is thicker than normal with much deeper rete pegs than usual, with hyperplasia of the basal cells and some irregularity of the nuclei. Also is to be noted the parakeratosis. The right half of the slide shows typical squamous cell carcinoma, a cornifying, slowly growing tumor, with epithelial pearls and large epithelial cells with pale cytoplasm. The parakeratosis in this area is prominent, and the invasive strands are obvious. A moderate chronic inflammation is present.

Stanley Way in England, makes a large U-shaped incision in the lower abdomen, extending widely to each side, and crossing above the mons. Excision of the inguinal and femoral nodes and the pelvic lymph nodes by extraperitoneal exposure are followed by wide excision of the vulva. This extensive operation has given sixty-one per cent five-year arrest, including its use in many rather advanced tumors.

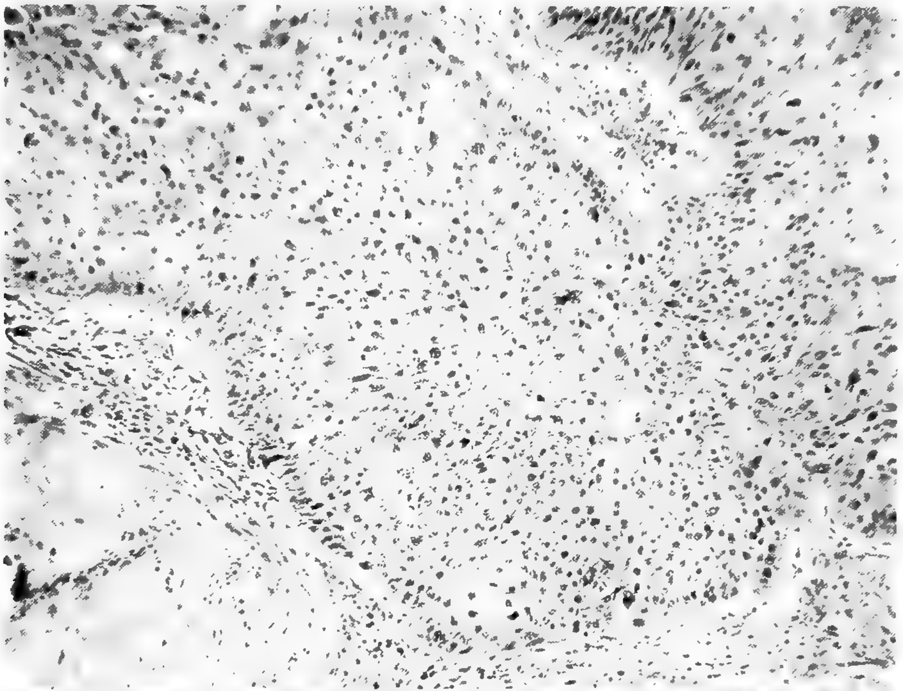
The lymphatics of the upper two-thirds of the vulva drain largely to the inguinal region. Therefore, it is logical to excise the regional nodes, especially when the tumor is situated in this area. But the lymphatics of the posterior third largely drain up along the rectum. Exenteration, removing the rectum, uterus and vagina, in addition to radical vulvectomy, has been performed in a few cases, because of this lymphatic drainage. It is doubtful that this heroic procedure will be used frequently, because of its scope and the hope that the carcinoma may not have metastasized in this direction.

Metastatic carcinoma does occur in the vulva. Cervical carcinoma metastasizes to the outlet and Bartholin's gland region. Adenocarcinoma of the endometrium occasionally metastasizes to the vulva, appearing as firm nodules. Metastatic chorion-epithelioma appears as purplish-red tumors, which may make their presence known first in the vagina or vulva.

Fibroma of the vulva

The rubbery or quite hard benign fibroma of the vulva may produce no symptoms, and at times is allowed to grow to great size by the anxious patient. Due to its weight, a pedicle of varying length may develop, so that the tumor may hang between the patient's legs when walking. Interference with the blood supply may produce superficial ulceration. Excision is especially simple when

Fig. 36. Squamous cell carcinoma of the vulva, composed of broad strands of invading cells, which appear to have intact borders and suggest the basal cells of the more superficial skin. However, this is truly invasive; the long strands of malignant cells show all of the individual malignant changes, including intra-cellular edema, giant nuclei, minute pearl formation in many areas, and marked abnormal changes in the nuclei.



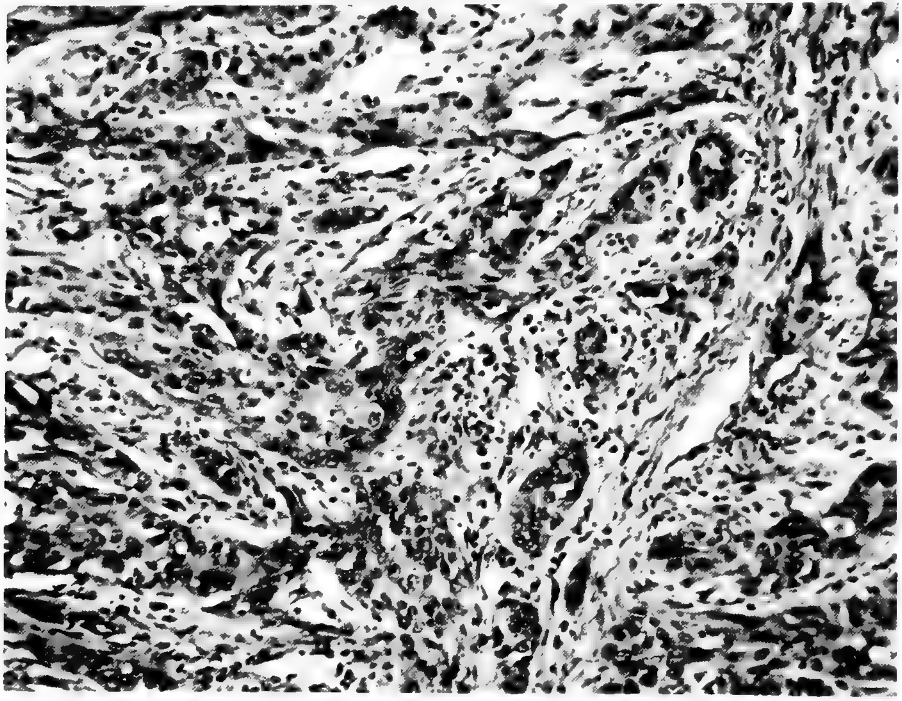


Fig. 37. Invading squamous cell carcinoma of the vulva. Here the invading strands are much smaller in width, but appear more vicious in their growth into the tissues. The strands are from one or two to four or five cells thick. The abnormalities and the variations in the cells are obvious. A slight to moderate chronic inflammation is present. This shows less pearl formation than many of the tumors of the vulva.

a pedicle has developed. A deeply placed small nodule may be involved in the normal and numerous small blood vessels of the vulva. Malignant change occurs very rarely.

Sarcoma

Sarcoma of the vulva is quite rare, and appears more as a fibrosarcoma, recurring locally after simple excision, but later extending generally. Lymphosarcoma also appears in the vulva, but is quite common.

Hydradenoma

Hydradenoma of the vulva is a benign adenoma of the apocrine sweat glands. It is yellowish in color and elevates the epidermis. Often part of the tumor protrudes from the hair-follicle opening as a small yellow granular projection. This tumor has a papillary arrangement of closely packed glands. Microscopically, it simulates malignancy, but actually very few malignant hydradenomas have

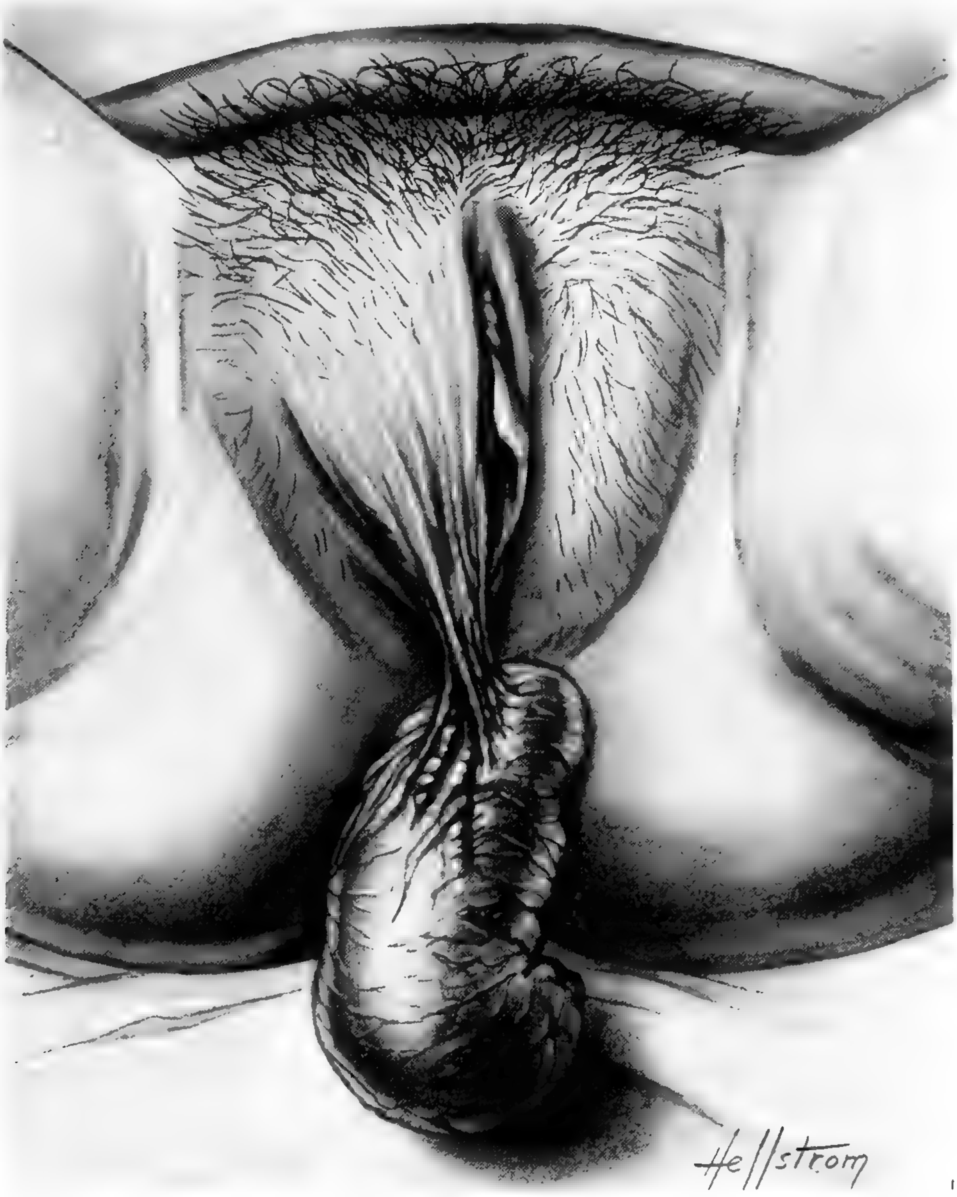


Fig. 38. Fibroma of vulva. A slowly growing, very firm tumor, with ulceration posteriorly (not shown). The long pedicle is produced by the weight of the tumor.

been reported in the literature. The tumor causes no symptoms. It is excised because it concerns the patient, and for accurate diagnosis by microscopic study.

Melanoma

Dark, pigmented moles of the vulva, are of particular importance, because of possible malignant change. Such black or dark brown moles of the vulva should be excised with a generous margin. Rarely, they will prove to represent malignant melanomas. Radical vulvectomy, with regional lymph node resection, then is indicated. Even though this malignant melanoma does metastasize often by way of the blood stream and make all therapy futile, cure may follow excision. Metastases may occur in the meninges and produce neurologic findings.

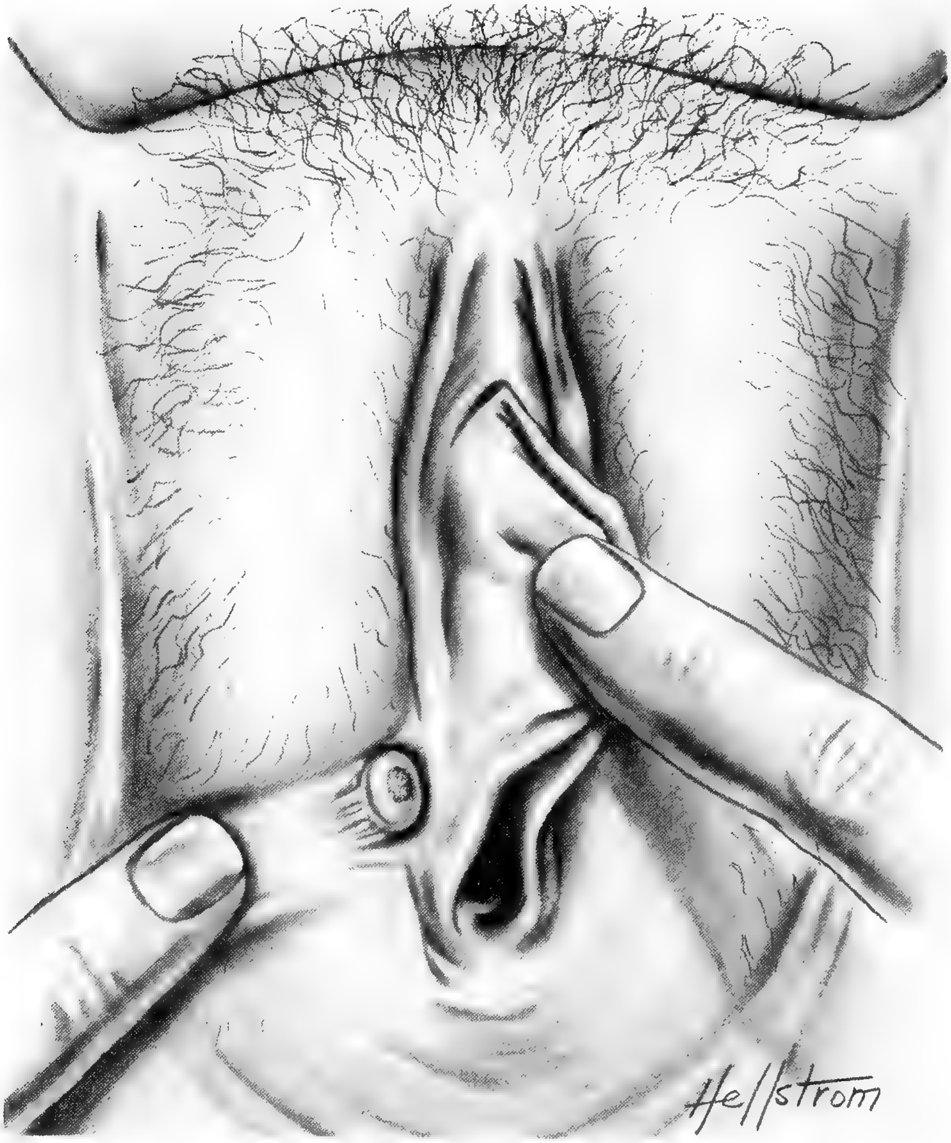


Fig. 39. Hydradenoma of vulva. A raised, yellow nodule, with some papillary tumor extending out the opening of the hair follicle. Benign and usually asymptomatic.

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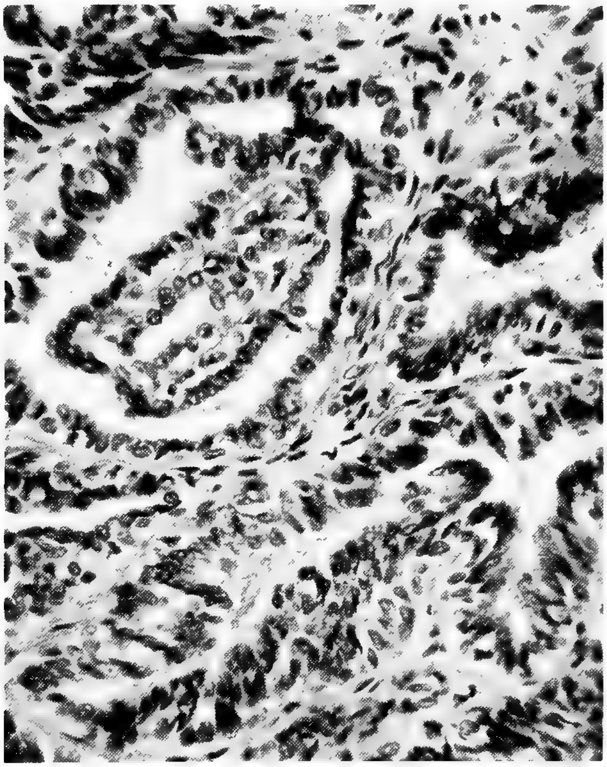


Fig. 40. Hydradenoma of the vulva. The papillary appearance of this tumor with infolding into the glands, the ragged appearance of the cytoplasm of the cells, and the piling up of cells, four, five, or six layers deep are characteristic of this tumor. The nuclei are relatively regular, though mitoses may be present. The thin strands of connective tissue stroma vary in degree in different tumors but usually are not obvious. As a rule this is a benign tumor.

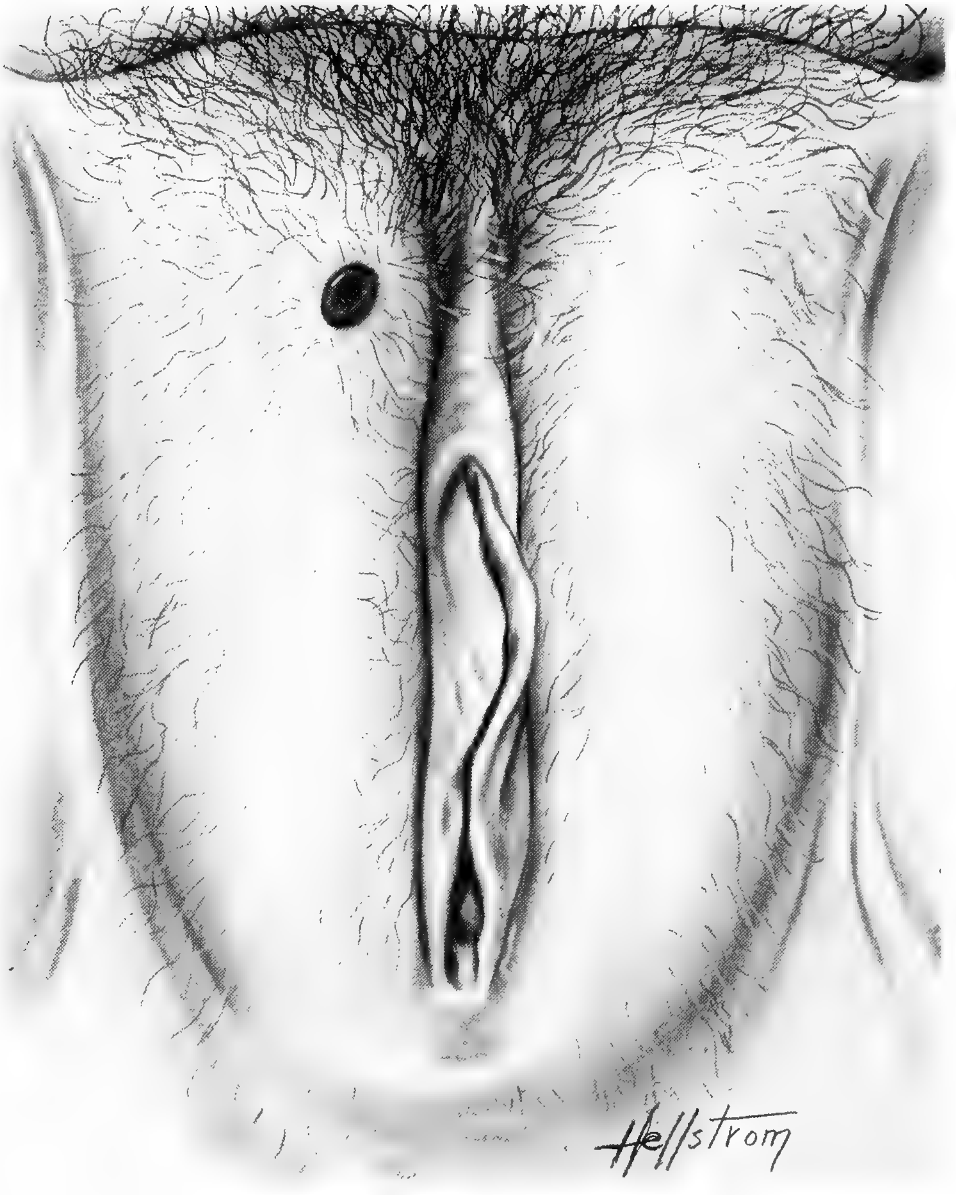


Fig. 41. Melanoma, right labium major. All pigmented moles of the vulva may be malignant, or become malignant. Metastases may occur early, particularly to the meninges.

CHAPTER IV

Diseases of the Vagina and Female Urethra

PREPUBERTAL VAGINITIS

At birth the vagina of the female infant is lined with a relatively thick layer of stratified squamous epithelium. This epithelium is essentially as thick as that in the vagina of the adult woman, although the cells appear less mature and do not reach the stage of semicornification of the adult. There are fifteen or twenty layers or more of cells at birth, resulting from a strong estrogenic activity. This effect is produced by the estrogen in the blood of the fetus, which is synthesized by the syncitial cells of its own placenta. Similarly, the breasts show an engorgement or slight development, some degree of firmness, and may produce a small amount of secretion a few days after birth, known as "witch's milk." The thickened vagina from the placental estrogens recedes ten days or two weeks after birth because the estrogens are rapidly metabolized in part, and the remainder excreted by the kidneys. The estrogenic effect disappears relatively rapidly in the course of two to six weeks. As the estrogenic level falls there may occur slight withdrawal bleeding from the endometrium. When sufficient time has elapsed, the vagina becomes thin and has five or six layers of stratified squamous epithelium of the immature basal cell type. The rugae of the vagina are indeterminate. Secretions from the vagina at this time contain small, round, or oval epithelial cells, representing the immature para-basal cells which are shed into the vagina. This is in contrast to the large hexagonal cells with very small nuclei which are shed immediately after birth, and in the vaginas of women during active ovarian function. Although the vagina of the infant and prepubertal child gradually enlarges and elongates as the individual grows, its epithelium remains quite thin. This state persists until estrogens begin to appear in the child's own body, mainly from her ovaries, but apparently in part from her adrenal glands, as puberty approaches. The effects of estrogen appear several months before the first menstruation, and sometimes two or more years earlier. The vagina of the prepubescent child or infant without estrogenic effect has a pH of 7.0 to 8.0. This neutrality or alkalinity is evidently responsible for the type of bacterial flora that appears in the vagina at this period of life. In contrast, the vagina affected by estrogen in the child just before puberty, or of adolescent or adult women, has a pH between 3.8 and 4.5, and the bacterial flora is quite different, if this acidity is maintained.

At birth the vagina is sterile. Within a few hours cocci and bacilli may be found. In the next few days Doderlein bacilli appear temporarily while the vagina remains acid and contains glycogen. After the vagina becomes thin, a variety of organisms invade the vagina, many of which, in all probability, come from the gastrointestinal tract. Accompanying these various bacteria are degrees of inflammation. Most of the time this inflammation is relatively slight, but it continues in some degree until the vagina thickens and becomes acid in the prepubertal estrogenic state, when denuded areas rapidly heal by proliferation of squamous cells. The acidity in the vagina apparently is produced by the fermentation of glycogen, which occurs in the desquamated, squamous epithelial cells. Actually, the glycogen probably is fermented by an enzyme to produce glucose, and the lactobacillus (Doderlein's bacillus) breaks down the glucose to form lactic acid. It is important to understand that degrees of inflammation in the immature vagina are so universal as to be usual, and perhaps even to be considered normal. The appearance of the vagina in the vaginitis of childhood is that of redness and hyperemia, of slight or moderate or marked degree. Inspection by the endoscope or small Kelly air cystoscope shows the walls of the vagina reddened as is the surface of the small cervix.

Eversions of the cervix are difficult to distinguish because of the similar pink or reddened appearance of the cervix as seen through the single layer of everted columnar epithelium and the thin layer of immature, non-glycogen containing, squamous cells. Washings of the vagina, which are most important in the estimation of vaginal disease and health at any age, are obtained by using the clean medicine dropper which instills normal saline solution back and forth. A drop is placed on the slide, to which is applied the cover slip. Under the microscope, the types of epithelial cells, number of polymorphonuclear leukocytes (pus cells), and presence of trichomonads and fungi, may be determined. The number of pus cells usually indicates the degree of inflammation present. Cultures of the vaginas of infants and pubescent children show a great variety of organisms. There are the *Streptococcus pyogenes*, colon bacillus, *Staphlococcus aureus*, etc. At times it appears that one organism is most prominent and most likely the bacterial agent in the particular case. Usually, the identity of the organism seems of little importance in the treatment. An exception is the very rare diphtheria of the vagina, suspected by the characteristic membrane, confirmed by culture, and treated by antitoxin and specific antibiotics. As a rule, in usual vaginitis of childhood, ridding the vagina of certain organisms by antibiotics is not the method of cure because recurrence is usually immediate, but cure is better established by causing the vagina to become thick, healing any ulceration, and producing acidity to destroy those neutral and alkaline-loving bacteria, by means of local hormone therapy.

For many years it has been known that much of the vaginitis of young children is related to and apparently caused by the *Neisseria gonorrheae.* Great concern developed over presence of the gonococcus in the vaginas of the young. All vaginitis in the child has been considered as suspect of gonorrhea. At one time large teaching hospitals maintained gonorrheal vaginitis clinics, widely attended, where treatment was carried out by all kinds of antiseptics, instilled daily, biweekly, or weekly. The cure rate was low and recurrence was high, causing exasperation on the part of all concerned, to say nothing of extreme fright in the young patients.

In 1933, Lewis demonstrated that the vagina of the prepubescent girl became remarkably thick and developed an acid pH, similar to that of the adult, after parenteral administration of estrogenic hormone. The estrogen thickened the vagina, produced acidity indirectly, and the gonococci quickly disappeared. This method of treatment was hailed widely, and elaborated upon by Te Linde and Brawner in 1935, when they used small suppositories of estrogen, which were inserted in the vaginas of young children over a period of several weeks, producing a complete change by local estrogen therapy. Subsequently, with availability of oral estrogens, both natural and synthetic, more often the treatment has been carried out by this means. However, estrogenic therapy has been associated with certain annoying effects, including soreness and tenderness of the breasts from the growth of subareolar breast tissue, the development of hair on the vulva, swelling of the vulva, and occasionally bleeding from the over-stimulated uterus and its endometrium. With the advent of the sulfonamides, and especially after the discovery of penicillin and other antibiotics, much of the treatment consisted of the use of these medicinals, particularly penicillin, for the purpose of destroying gonococci or other pathogenic bacteria. It was soon learned that the non-gonorrheal vaginitis is helped little by antibiotics, and that the gonorrheal vaginitis commonly recurs rapidly. In 1942, an important paper appeared by Cohn, Steer, and Adler, of the Public Health Department of the City of New York, which indicated that the treatment of gonorrheal vaginitis of children, and incidentally other forms of vaginitis, too, was greatly over-emphasized, that it was of no serious importance to children, except for inconvenience and annoyance, that the communicability, while evidently frequent in the case of the gonococcus, was nevertheless not serious. They advised that cleanliness, Sitz baths and loose garments be urged in place of interminable injections, instillations and strenuous treatments. This attitude de-emphasized the importance of vaginitis in children, and properly so, although perhaps to a greater degree than necessary, as the symptoms do include burning in the vagina, itching, frequency of urination, pain in the deep part of the pelvis, and annoying discharge on the clothing with odor, all of which deserve treatment.

In a public clinic, it seems that in twenty-five per cent of cases of vaginitis in children the etiologic agent is *Neisseria gonorrheae.* Just why the more serious complications are not more frequent is not understood. It is true that, in rare instances, gonococcal salpingitis and pelvic peritonitis may occur in the very young girl, but certainly the occurrence is very unusual, in consideration of the number of cases with gonorrheal vaginitis. That gonorrheal ophthalmia is very uncommon is also a mystery, because obviously young children with burning and discomfort in their vagina would be inclined to touch the area with their hands, and subsequently brush away those childhood tears or clear sleepy eyes with the same unwashed hands. That gonorrheal ophthalmia does occur is well known, but it is rare under these circumstances.

The epidemiology of vaginitis caused by *Neisseria gonorrheae* in young girls is unknown. The method of acquiring and transmitting the infection is not clear. It is assumed that it may be transmitted from toilet seats, from clothing, from towels, or from mothers, nursemaids, or even from playmates. But certainly, no definite evidence of the method of transmission has ever been made clear. Gonorrheal infection of the post-pubescent girl is thought never to be possible without sexual relations. It is also interesting that gonorrheal vaginitis in the post-menopausal woman, where the vagina becomes very similar to that of the prepubertal child, is extremely rare.

A few years ago Weaver of Texas presented an intriguing paper, suggesting that a large percentage of those children considered to have gonorrhea, actually have an infection caused by *Neisseria sicca,* a similarly appearing organism with slight fermentative differences on culture. The latter organism is not considered to cause a venereal disease. Further study after this presentation has failed to show that the *Neisseria sicca* occurs with any frequency in the vaginas of children, but does show that the *N. gonorrhea* is the infective agent in a definite percentage of cases.

That vaginitis in childhood may be caused by the pinworm has been a matter of some debate and interest. Pinworm infestation of the gastrointestinal tract is extremely frequent in occurrence. The worms come out of the rectum and lay their eggs in the anal folds during the night, and then retreat into the rectum. Later the eggs are transposed to the child's mouth and swallowed again. This causes the infection to be continuous over a long period of time. It has been thought by many, because of the frequent occurrence of pinworms, that they may extend into the vagina and cause vaginitis. The worm or the egg may be found in the vagina in very rare circumstances, but examination of a large number of children with pinworm infection has indicated that this is an unusual occurrence. It would seem that pinworm vaginitis must be very rare.

Another form of vaginitis is that caused by foreign bodies. The infant, in particular, has a natural tendency to explore the external genital organs, and to press various objects in these areas, so that occasionally one finds foreign bodies in the vagina. These may include match sticks, bobby pins, safety pins, pieces of chalk, paper, stones, or any conceivable small object, which a child might be able to insert. The presence of foreign objects in the vagina is uncommon, but one may be found on occasion and is to be considered in each case of vaginitis. As a rule, the physician would examine the patient externally, study the fresh preparation for the presence of pus cells, note if there is any apparent foreign body by contact with the medicine dropper, and perform a rectal examination to determine the presence of any mass and to determine the apparent normalcy of the pelvic organs. Any suspect foreign body might be elucidated by the x-ray film, but further inspection and investigation of the interior of the vagina usually is not performed until the painful vaginitis is improved by therapy. After treatment for a reasonable period of time, if vaginitis persists, certainly one should investigate the interior of the vagina with the endoscope, or the Kelly cystoscope, best performed in the knee-chest position, using the head mirror for vision.

The treatment of vaginitis in children first includes reassurance. Because the mild degrees of redness and slight discharge may be controlled by tub baths, loose clothing, and the application of cold cream occasionally to the vestibule, it is important that the mother understand that some degree of redness occurs in essentially all little girls, that it appears in variable degree until the child reaches the estrogenic state, either the prepubescent estrogenic state or the postmenarchal degree of maturation. If the vaginitis is of annoying degree, and usually it is more annoying to the mother, estrogens may be used in any of its various forms, by hypodermic injection, oral tablets, vaginal suppositories or local cream. Lately estrogen creams have been more popular, being applied to the vestibule and vulva, having the soothing effect of a cold cream and causing thickening of the vestibule and entire vagina. While there are many estrogenic creams available, including the synthetic estrogens, one containing conjugated equine estrogens (Premarin) seems particularly efficacious. Such a cream is applied locally each night for two weeks, then on alternate nights for two weeks, then once or twice weekly for a month or two. As a rule this treatment causes the vagina to develop a full estrogenic thickness within two weeks. The pus cells quickly disappear. Gonococci and other pathogenic organisms are eradicated in two to four weeks. The vagina then has the Doderlein bacillus as its new inhabitant, but in addition staphylococci, a few E. coli, and a few other organisms may be present without inflammation. As the cure of the vaginitis proceeds, especially if the estrogens are present in any excess, varying amounts of white mucus appear, its appearance derived from the profusion of large hexagonal, glycogen-containing, squamous cells. This mucous discharge may be more marked than the original purulent discharge. When annoying, the estrogenic therapy has been excessive. Excessive local use also may cause edema of the vulva. Even more excessive use may cause some enlargement of the breasts, with tender "buttons" beneath the nipples. It is preferable to reduce the frequency of applications, to continue only a mild estrogenic effect. After two or three months, the estrogens are discontinued. The mother may determine from any recurrent redness that local treatment may be used again as indicated, but not to the extent to produce the heavy white discharge of epithelial cells. This estrogenic effect, with its concomitant acidifying action, usually removes all of the inflammation from the vagina. A slight degree of eversion of the columnar epithelium commonly occurs in young girls, but inflammation of the cervix rarely is important in vaginal infection in childhood. Occasionally there is eversion with inflammation, and local applications of silver nitrate through the Kelly cystoscope in the vagina may be helpful. It would appear that cultures are unnecessary in the treatment of vaginitis in children, that antibiotics and sulfonamides are unnecessary, and that local estrogen creams used intermittently give satisfactory results.

Occasionally, children nearing puberty, and even a few years before puberty, are brought to the physician because of vaginal discharge, in which the finding is that of mucus, containing a profusion of large hexagonal squamous cells without pus cells. In this instance, the mother is to be reassured that this is a normal estrogenic effect, produced by the child's own hormones, and that no treatment is necessary. Usually there are signs of breast stimulation and growth of vulvar hair in these cases.

INFLAMMATIONS OF THE VAGINA DURING MENSTRUAL LIFE

There are two particular infections of the vagina during menstrual life, one caused by the *Trichomonas vaginalis,* and the other caused by *Candida albicans.* A third group has been called non-specific vaginitis; a fourth must be mentioned: *Haemophilus vaginalis* vaginitis.

The protozoan, *Trichomonas vaginalis,* is an enigma. Its life-cycle is not completely understood. Apparently it is responsible for an extremely common inflammation in the vagina. It occurs almost entirely during menstrual life, or in the thickened fully-estrogenized vagina. It does occur in young children, though in very rare instances, probably in only one per cent of cases of vaginitis of childhood. Occasionally this infection occurs after the menopause in an atrophic vagina, but this again is relatively uncommon. It was formerly believed that this protozoan may extend into the vagina from the rectum, that it may represent a morphological change of the *Trichomonas hominis* but this has never been demonstrated. It has been suggested the *Trichomonas vaginalis* vaginitis is a venereal disease, transmitted only, or usually, by sexual intercourse. This has never been proven; at least there are exceptions. Suggestions have been made that the disease is transmitted to women by their husbands, and that difficulty in cure persists because of frequency of the organism in the prostatic secretions of the husband, cure being prevented or delayed by re-infection. Again this seems largely hypothetical, and varying observers have given different opinions.

Karnaky has written many papers on vaginitis and has made important contributions. It has been his opinion that there are only two types of vaginitis, one due to *Trichomonas vaginalis* and the second due to *candida albicans,* that the non-specific vaginitis is a term used when one of these two offending organisms are not found on one or two observations. Cultural studies have shown that, in many so-called non-specific cases, one or both of these commonly occurring etiologic agents are present. The more one studies the case with so-called non-specific vaginitis with repeated observations, the more frequently one finds either the trichomonad or the fungus.

After admitting that the origin of trichomonal infections is unknown, it is uncomfortable to relate that the treatment is entirely imperfect. But first, the symptomatol-

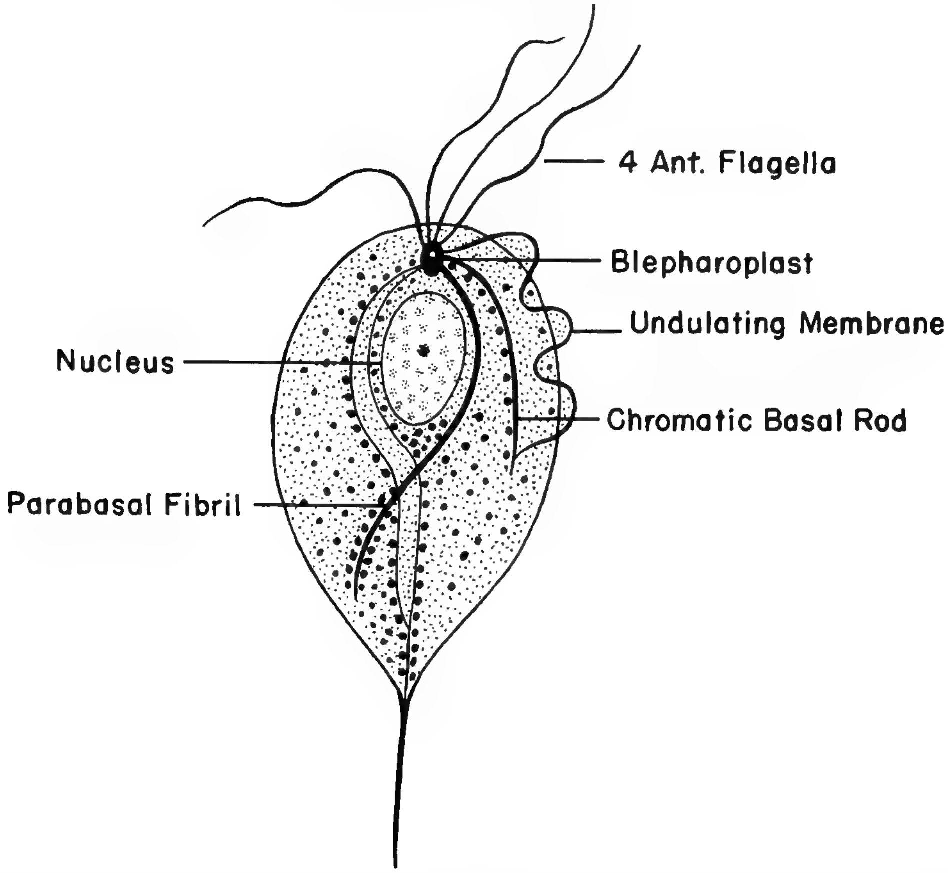


Fig. 42. The trichomonas vaginalis. This flagellated protozoan is associated with more cases with vaginitis than any other organism. In spite of its great prevalence, its life-habits are not understood.

ogy and pathology must be elucidated. The patient with *Trichomonas vaginalis* vaginitis may have no complaints. In fact, although this organism is found in about ten per cent of all women who are not pregnant, and in about thirty per cent of women who are pregnant, in a fair percentage there are no real symptoms. A closer questioning does reveal, as a rule, some discharge and a slight irritation which the patient hesitates to mention, or which has not previously brought itself to her attention. Such patients have been called "carriers," but they are to be considered cases with mild chronic vaginitis. The next group of those infected with this organism complain of chronic discharge, not severe, but annoying over a period of years. Here again the organism and moderate pus cells are found, but the symptoms are not marked. In the third group there is the acute fulminating case of *Trichomonas vaginalis* vaginitis. The vagina becomes very red and irritated. This redness extends into the vestibule. Occasionally the entire labia minora and majora are involved, with much edema, with intense redness, and a profuse yellow, sometimes foamy, discharge, which drips from the vagina. This patient has miserable complaints of burning and pain in the vagina, and frequency and burning of urination, discharge, severe dyspareunia, and intense itching of the vulva. Such pruritus, even in the chronic and less inflamed cases, commonly extends about the anus, where it may be more marked.

Usually, one considers that the vaginal wall is the primary involvement of this disease, and it is true that the wall shows varying degrees of redness, and biopsy shows definite subepithelial inflammation. On the cervix, there appear typical small red spots, and sometimes on the upper vaginal wall, which are very characteristic of the infection of *Trichomonas vaginalis* vaginitis ("strawberry vagina"). Microscopic examination shows minute abscesses in the red spots, with marked accumulation of polymorphonuclear leukocytes, with necrosis and destruction of the stratified squamous epithelium. These are very minute but very characteristic. It is also important to realize that varying degrees of cervicitis, both acute and subacute, are produced by the *Trichomonas vaginalis.* Sometimes the cervix is quite edematous, with severe eversion and erosion, and one would think that never could such a cervix heal with simple anti-trichomonal medication, but that most extensive cauterization would be necessary eventually; yet complete healing and a normal appearance may follow vaginal suppositories. Often the trichomonad is superimposed on eversive cervicitis, and more often further treatment by cauterization is necessary. The *Trichomonas vaginalis* involves Bartholin's gland and Skene's ducts of the urethra very frequently, and has an indirect relation to most of the inflammations of these appendages. Acute infections of the Bartholin's gland, with abscess formation, are very commonly associated with *Trichomonas vaginalis* vaginitis. When one milks the urethra, as is done in routine pelvic examinations, and a drop of pus is obtained, often the trichomonad is present within the secretion. The urethral caruncle may be caused by the trichomonad infection, and is relieved by trichomonacidal therapy to the vagina. This is the caruncle found during menstrual life; the postmenopausal caruncle rarely is associated with trichomonas infection.

The treatment of *Trichomonas vaginalis* infection is not entirely satisfactory. Apparently there are available over one hundred preparations for the treatment of this disease; in each instance, the manufacturer indicates that a remarkable cure awaits her who uses his product. The time-tried products, diodoquin (Floraquin, Searle) and acetarsone (Devagan, Winthrop) represent the best treatments in the writer's experience, although every gynecologist is constantly looking for a better therapeutic agent. Because of dissatisfaction, he may tend to make his office a workshop to try various new medicinals, but commonly each brings disillusionment. Many methods of treatment suggest local application by the physician three times weekly for varying periods of time. These include cleansing the vagina, applying solutions and paints, blowing in powders, the prescribing of oral medication, and the administration of special douches. However, it seems that all these fancy ministrations give no better results than the simple application of a tablet or suppository. At one time, the author conceived of a treatment with ice-water douches, because the trichomonad becomes immobile quickly when outside the warmth of the body. The treatment was not acceptable because of the great discomfort from the ice water in the vagina, but the vaginitis did seem improved. Higgins recommended insertion of aspirin tablets in the vagina, indicating that they were efficacious. A standard treatment is that of the application of a starch tablet containing acetarsone each night for ninety nights. It is quite necessary that the tablet be applied during menstruation, as the organisms multiply particularly during that time, and recurrence after menstruation has been extremely frequent. Instillations of the urethra and Bartholin's gland seem unnecessary, if the treatment to the vagina is prolonged sufficiently. Cauterization of the cervix when indicated may be helpful in the final result. Unfortunately there are recurrences in ten to twenty per cent of patients even after prolonged treatment, and some patients with a history of the disease for several years are given symptomatic relief but seem impossible to cure. Undoubtedly the answer to therapy will appear, and probably it will clarify our understanding of this annoying inflammation.

Fungus infections of the vagina are less common than those due to the *Trichomonas vaginalis,* and yet of sufficient frequency to cause an annoying degree of discomfort in many patients. *Candida albicans* may be present without any symptoms in the vaginas of many women. In a series of one hundred patients we found this organism by culture on Nickerson's medium in twenty-six patients, but only two had complaints and signs of vaginitis.

It is apparent that *Candida* occurs frequently on the vulva and in the vagina without symptoms, and it seems that inflammation with itching, burning, and characteristic "cottage cheese" type of discharge, may be related to allergy to the fungus, to lack of immunity to the organism, or to some other unknown factor. It is well known that the fungus thrives in the vagina of the diabetic (and every patient with fungus infection should be carefully checked for diabetes), presumably because there is increased glucose in the secretions of these individuals, or at least sugar is deposited on the vulva and about the vaginal orifice from the dried urine. Rarely the organism is found in the prepubes-

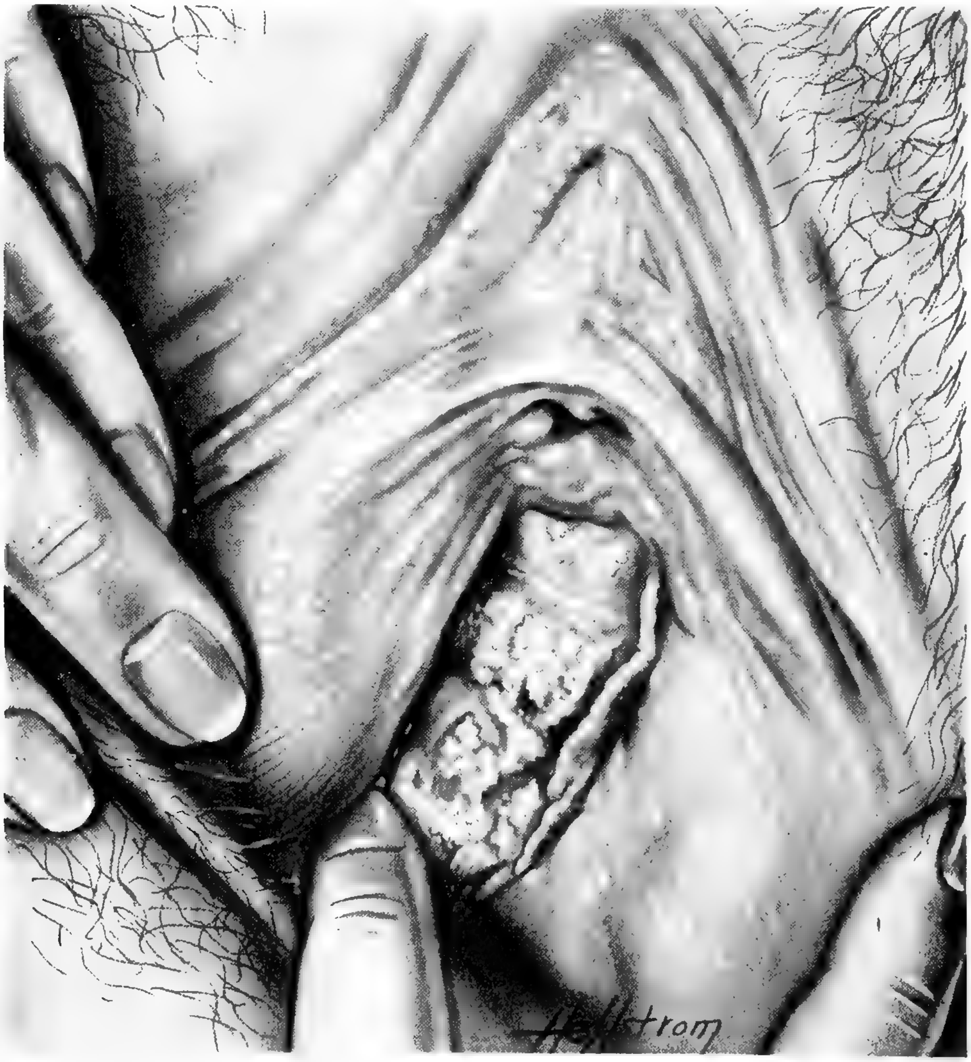


Fig. 43. Candadiasis, fungus vaginitis, monilia vaginitis. The cystocele and rectocele are covered with cottage cheese-like material, composed of agglutinated epithelial cells and intermingled mycelia.

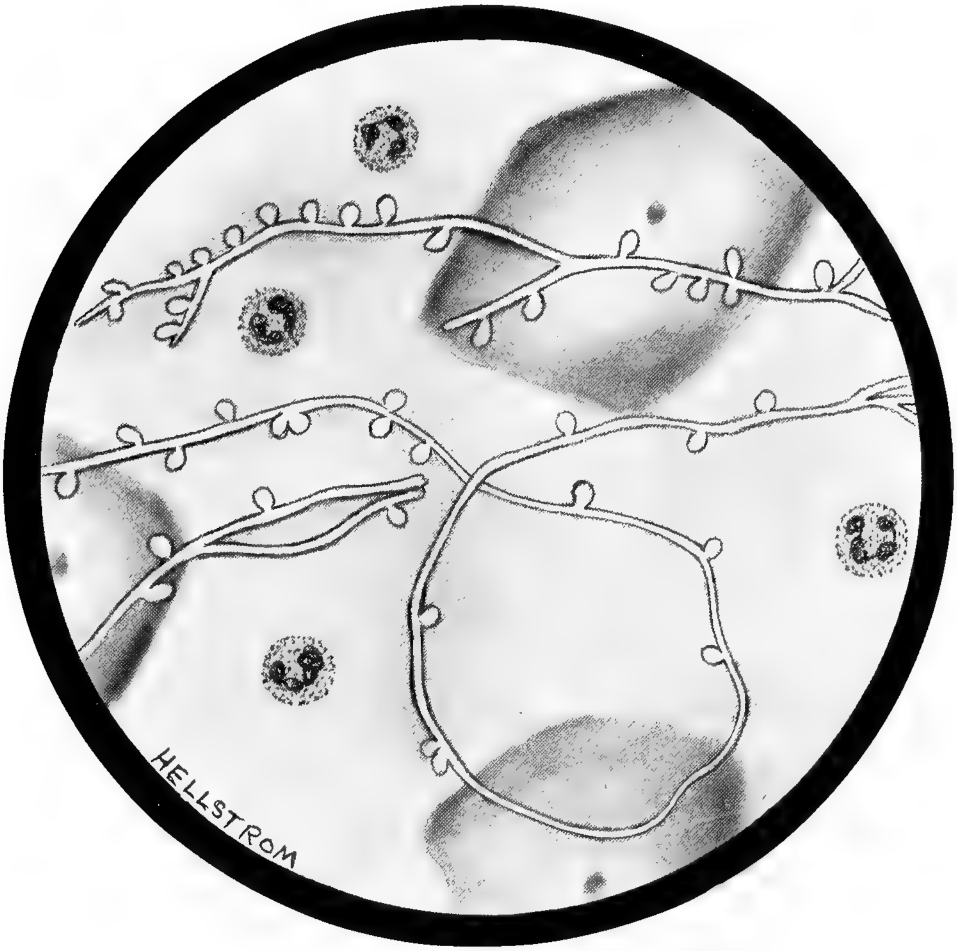


Fig. 44. Mycelia of candida albicans. The small buds are readily seen. This translucent organism may be seen in the fresh preparation, but concentrated study through the microscope is required. Gram's stain and cultures are adjuncts for diagnosis.

cent vagina, and uncommonly it is found in the post-menopausal vagina. The *Candida* often may be cultured from the vulva of the woman with pruritus vulvae, but its etiologic significance may be doubtful. Inflammation in the vagina may be very slight, producing little or no discharge, and only minor itching about the vagina and vulva. In other instances there is profuse cottage-cheese discharge, severe burning, pain in the vulva, burning on urination, marked itching about the introitus, and very distinct redness of the vaginal walls.

The best treatment in former years was the application of gentian violet. This continues to be a good treatment, and gentian violet has been prepared in a cream base. During World War II, propionic acid compounds were used for various fungus diseases of the skin. Later it was learned that good results followed its application to the vagina for fungus infection (Propion-Gel). Sometimes this treatment has seemed uncomfortable in the acute phases. Phenylmercuric acetate, in a jelly, often is a quite satisfactory treatment for fungus infection of the vagina and vulva (Nylmerate). Recently the antibiotic, nystatin (Mycostatin) has been used in suppositories and local ointments, especially in stubborn cases, with very satisfactory results.

It is to be noted that fungus infection in pregnant women, as in the case of *Trichomonas vaginalis* vaginitis, is extremely resistant to any cure. As a rule, only improvement can be obtained. A complete cure rarely occurs until after delivery.

Non-specific vaginitis has been a wastebasket term for years, and has included all the cases in which the *Trichomonas vaginalis* or *Candida albicans* could not be found. Actually this makes up a rather small percentage, because the industrious approach usually will find one or the other. Often one will have treated *Trichomonas vaginalis* infection with little or no improvement, only to find there is an associated fungus infection, which requires a different chemotherapy. Some years ago the *Streptococcus subacidus* was thought to be the important cause of vaginitis, far more important than the *Trichomonas vaginalis* (Hibbert and Falls, 1938). But after several years this work was not substantiated and has been forgotten. It is doubtful that there exists such a disease as non-specific vaginitis. Possibly filterable viruses may cause inflammation in the vagina, but very little work has been done in this field.

Haemophilus vaginalis vaginitis. In 1954, Gardner and Dukes presented their thesis that a larger percentage of cases with vaginitis than those caused by the *Trichomonas* was caused by a small hemophilus bacillus. Usually in the odorous secretion there was no pus. The patients complained of burning and discharge. There was no inflammation in the walls of the vagina. This concept and this organism have not met with corroborative findings over the country. A few investigators have claimed to have confirmed this work, but others have failed to isolate this organism in their cases, and even doubt its very existence. Many have felt that a discharge without pus or inflammation could not be termed vaginitis. Varying treatments, including tetracylene and local applications, have been said to cure this

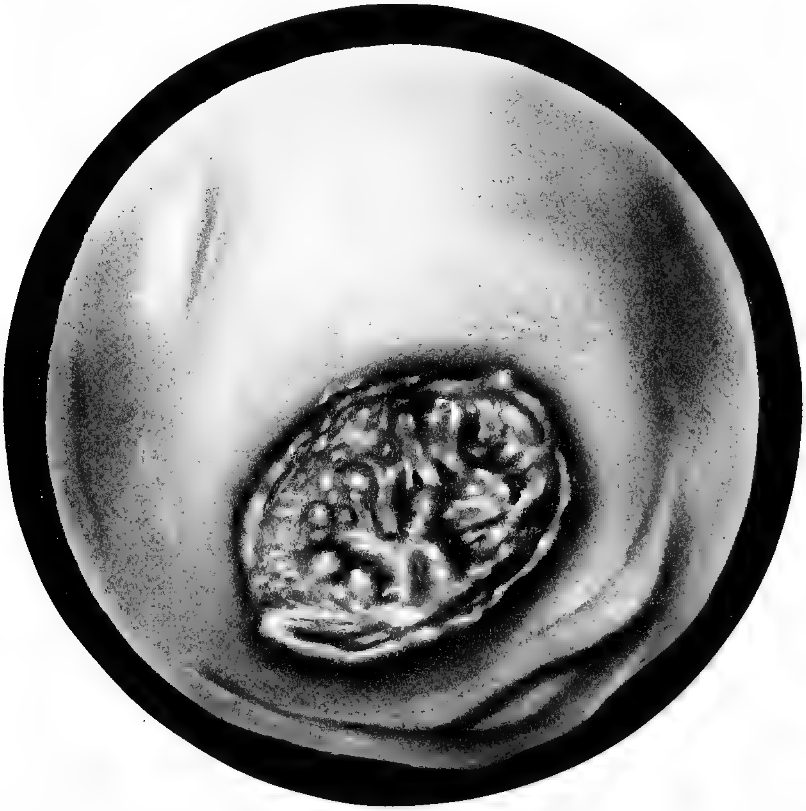


Fig. 45. Superficial ulcer on atrophic vaginal wall. Smears and culture showed candida albicans. This is unsuual.

disease rapidly. It has been diagnosed by the presence of the "clue cell," the fragmented epithelial cell with minute granulations throughout its cytoplasm, thought to represent the Haemophilus vaginalis organism. Doubt as to its authenticity persists.

POST-MENOPAUSAL VAGINITIS

Post-menopausal vaginitis is of almost universal occurrence in those women who have reached the post-menopausal state. After the menstrual periods cease, the ovaries usually gradually cease to secrete estrogenic hormone. This may occur over two or three months, or more slowly, over a period of two or three years. The atrophic changes do not follow necessarily immediately. Perhaps some of the prolonged estrogenic effect is derived from secretions of the adrenal cortex; this seems quite likely, as in some women the estrogenic effect persists many years after the natural menopause or even after the ovaries have been removed. Eighty or ninety per cent soon arrive at the time when the vagina becomes thin, lined with four to eight layers of relatively immature epithelial cells, the basal and para-basal cells which have not become mature and cornified, and which are shed into the lumen as round and oval epithelial cells, as seen in the fresh preparation or in the stained slide. Because of this thinness and associated neutrality or alkalinity, varying degrees of inflammation develop. Apparently this inflammation is related to trauma, the simple contact of the walls of the vagina, and to the various bacteria, which are of numerous types, similar to those found in prepubescent vaginitis. These include the colon bacillus, *Streptococcus pyogenes, Staphylococcus aureus* and many others. *Trichomonas vaginalis* is a relatively rare inhabitant, apparently preferring estrogen and glycogen; nor is the occurrence of fungus frequent, since glycogen and its hydrolyzed product glucose are needed for its growth. While some degree of vaginitis is the rule after the menopause, it is most important to the patient when it produces dyspareunia, which occurs especially in the nulliparous woman, the patient with good episiotomy after delivery, or the one who has had repairative surgery with reduction of cystocele and rectocele, so that the vagina has a snug orifice. In these instances, the atrophy and shrinkage produce prompt complaints. The mild or moderate inflammation augments the discomfort from the thinness as a cause for disappearance of libido, and certainly the complaint of dyspareunia. Nothing destroys interest in sexual intercourse as much as pain. While there may be numerous causes of loss of libido, not the least is post-menopausal vaginitis. Even in women with large cystoceles, rectoceles and marked relaxations, there may occur dyspareunia, symptoms of burning and irritation, and watery discharge. At intervals, there is bloody discharge caused by irritation of the thin and inflamed vagina. Often the patient has burning discomfort which she feels is in her rectum, and she may consult the proctologist who finds no disease. She may attend the urologist because the burning sensation seems in the area of the bladder or urethra. Often it really is in the bladder and urethra and is related to the atrophic changes in the transitional epithelium of the urethra and bladder, especially the trigone; this atrophy may allow mild inflammation and cause pain, burning and frequency of urination.

Atrophic vaginitis is treated by replacement of estrogens. This may be accomplished by hypodermic injection, oral ingestion, vaginal suppositories or vaginal creams. In these days the hypodermic injection is rarely used, because of the up and down effect, greater expense, and always the minute risk of infection or reaction. Oral medication is indicated if the patient has hot flashes and nervousness, as evident symptoms of the menopause. But if there are contra-indications to systemic therapy, such as the presence of asymptomatic fibroid tumors, a tendency to vaginal bleeding after small oral doses, or the presence of certain malignancies, treatment is by local administration. This may be accomplished by various suppositories of estrone or stilbestrol, but is particularly well treated by a vaginal cream containing conjugated equine estrogens (Premarin) which is applied in small amount once or twice weekly indefinitely, or as desired. The vagina rapidly thickens, the inflammation disappears, the burning discomfort is abated, and even the orifice, as in experimental animals, opens. Excessive use causes edema of the vulva, and occasionally some tenderness of the breasts, indicating some degree of systemic absorption. It is definitely important not to over use the estrogen, because the congestion from too much hormone may prove quite uncomfortable.

TUMORS OF THE VAGINA

Vaginal tumors include benign vaginal cysts, benign solid tumors, and malignant tumors, both primary and metastatic.

Vaginal Cysts

The Gartner's duct cyst arises from the vestigial wolffian duct which extends from the paroophoron in the broad ligament alongside the uterus, closely approximating the cervix, and down the side of the vaginal wall to the region of the hymen. In the vast majority of patients this remnant is never symptomatic during the life of a patient, but in some instances a cyst does develop in the duct along its course. Ordinarily this cyst is a singular one, is placed in the antero-lateral portion of the vagina at any area from the level of the cervix down to the hymen. It may vary from a few millimeters to four to six centimeters in diameter. It contains a clear, mucoid fluid, is lined by a single layer of cuboidal or low columnar epithelial cells, sometimes ciliated, and occasionally is lined with a thin layer of squamous epithelium. Malignant change in the Gartner's duct cyst must be of extra-ordinary rarity, although there are reported malignant tumors developing from adenomatous changes along the duct in the region of the external or lateral border of the cervix uteri. These para-cervical tumors also are quite unusual. Occasionally there is more than one cyst along the course of the duct, and rarely there are numerous cysts in each side wall of the vagina, beneath the bladder and over the rectum. Presumably these in the latter locations have the same origin from the wolffian duct, although their position is difficult to explain.

The Gartner's duct cyst ordinarily causes no symptoms, but when it becomes of considerable size, symptoms of pressure, frequency of urination, a feeling of fullness, especially in the sitting position, and discomfort on intercourse may occur. Small cysts that are asymptomatic need no treatment. In fact, the excision of these cysts, especially those high up near the cervix may be performed with difficulty, because they may extend rather far laterally from the vagina, and particularly upward around the side of the cervix in the region of the uterine vessels. On occasion, especially when there are multiple cysts, one may decompress them by the acutal cautery and produce a fenestration or prominent opening, which drains the mucus secretion and allows collapse of the cyst. If the window remains open as it should, the defect will always be noticeable, and yet cause no difficulty.

Inclusion cysts of the vagina are rather frequent in occurrence, being caused by an overlapping of the squamous epithelium in the spontaneous healing of a vaginal tear from delivery, or from the overlapping of squamous epithelium in episiotomy, perineorrhaphy and other vaginal operative procedures. If the squamous epithelium is included beneath the surface there may develop a small cyst, one, two, or three centimeters in diameter, lined with squamous

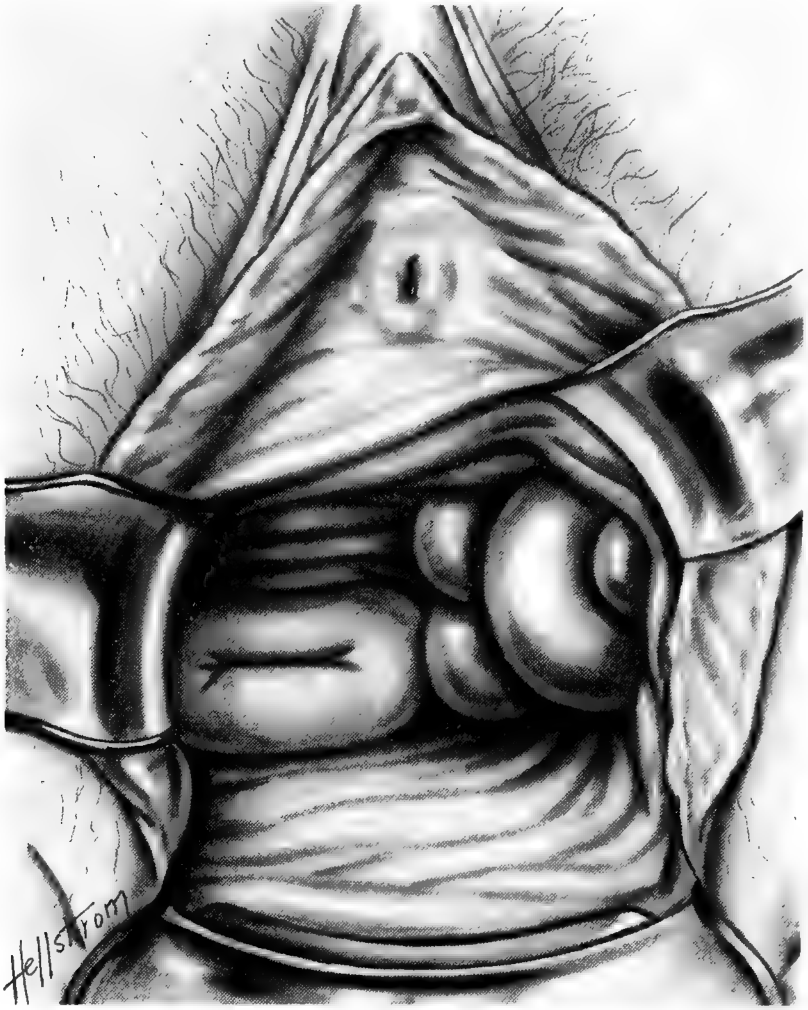


Fig. 46. Multiple Gartner's duct cysts along left side of vagina. Usually singular. They may occur on one or both sides, rarely in multiple areas over the vagina. As a rule, asymptomatic and have no complications. Excision of small cysts is not indicated.

epithelium and containing a yellow grumous material within the interior. These cysts occur particularly near the orifice of the vagina, and may cause discomfort and dyspareunia. Occasionally they become infected, causing pain and subsequently draining purulent material. If symptomatic, they are excised readily, care being taken not to injure the underlying rectum.

Endometriosis of the vagina may appear occasionally as minute, bluish cysts behind the cervix in the posterior fornix. The tissues deeper than the cysts are quite indurated. The infiltration in the cul-de-sac produces a characteristic irregular sensation to palpation. Endometrial cysts, a few millimeters or one centimeter or more in diameter, may occur after the healing of vaginal lacerations or incisions performed for various reasons, and particularly following excision of Bartholin's gland. Vaginal endometriosis has been recorded several times in the recent Swedish literature after incision in the vagina, when vaginal hysterotomy has been used for therapeutic abortion. More frequently minute areas of endometriosis appear in the vagina as red spots. These suggest, grossly, telangiectatic hemangiomas of two or three millimeters in diameter. These are not cysts, cause no symptoms, but are very evident to the inspecting physician. Vaginal endometriosis in the cul-de-sac is not approached for vaginal excision as a rule. On occasion one may excise these areas in the cul-de-sac, rectosigmoid and posterior vagina by the abdominal approach. Endometrial cysts occurring in vaginal incisions are treated by re-excision. Endometrial implants on the vaginal wall, appearing as red spots, may be excised or remain under observation.

Benign Solid Tumors of the Vagina

The benign solid tumors include the myoma, the fibromyoma and adenomyoma. The former two evidently represent a similar tumor, as varying degrees of fibroblastic tissue intermingle among the muscle cells. These benign tumors are quite uncommon but are seen on occasion, appear as hard, encapsulated nodules a few millimeters or several centimeters in diameter. The symptoms depend on the size of the tumor and pressure effects. Treatment obviously is by excision through the vaginal approach. Adenomyoma of the vagina also is extremely rare, is even more rare than myoma, and represents endometriosis with marked stromal reaction, including smooth muscle.

Malignant Tumors of the Vagina

Carcinoma of the vagina is a squamous cell cancer, arising on any portion of the vaginal wall. In the beginning it appears as a slightly raised, granular, white area, often warty, having a firm or hard texture, It spreads out onto the vaginal wall and later into the paravaginal tissues. When present on the anterior vaginal wall, the base of the bladder is rather rapidly involved. Similarly when present on the posterior wall, it may soon involve the rectum. Squamous cell carcinoma, or epidermoid carcinoma (since it is less cornified as a rule than the more adult horny tumors from the external skin), behaves much as carcinoma of the cervix, spreading in the lymphatics to the sides of

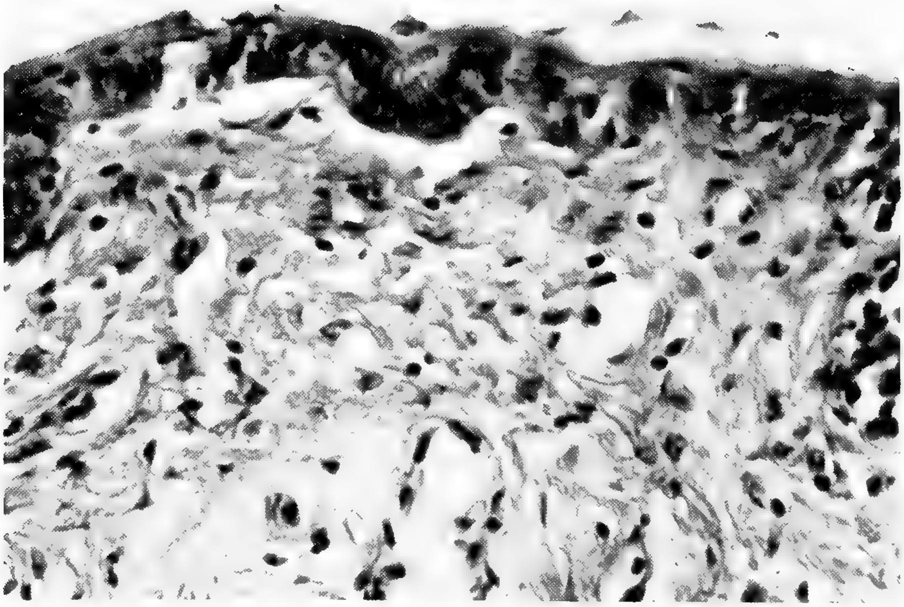


Fig. 47. Gartner's duct cyst. The lining is composed of low columnar cells, distorted by the pressure of the fluid on the interior of the cyst. In the wall are seen many small blood vessels. No malignancy is associated.

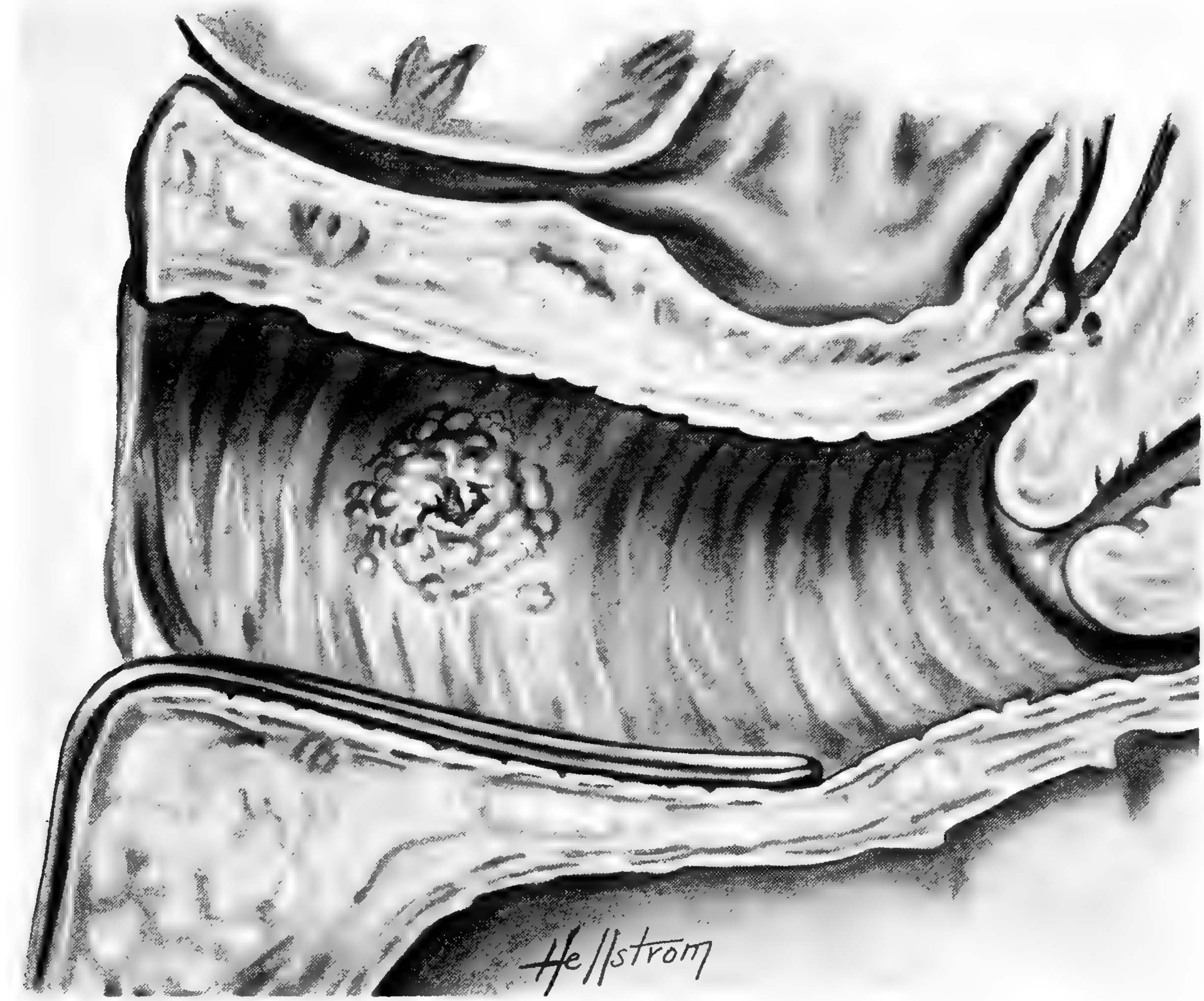


Fig. 48. Squamous cell carcinoma of the vagina. A raised, slightly nodular, firm growth, which tends to ulcerate and bleed easily. It occurs more frequently on the anterior or posterior wall.

the rectum and bladder, into the broad ligaments and into the lymph nodes of the sacral area, the obturator foramen, and on into hypogastric lymph nodes, external iliac nodes and up along the aorta. This squamous cell tumor, even less frequent in occurrence than the relatively rare carcinoma of the vulva, has been treated as a rule with the local application of radium, preceded or followed with deep x-ray therapy. Treatment has been notoriously poor, probably because the irradiation therapist hesitates to give the large doses that may cause fistulas of the bladder or rectum. The reactions of cystitis and proctitis are of major importance in disability.

Local excision of the carcinoma of the vagina is rarely of any value, the tumor having spread in the lymphatics beyond the line of excision, and beyond the relatively thin vaginal wall. Radical excision, as a rule, means removal of not only the pelvic organs and vagina, but either the bladder or rectum, depending on the position of the tumor, and perhaps both of these organs. The better approach today would seem to be by means of irradiation therapy, with the local application of radium, followed by deep x-ray therapy, because a few of these tumors at least are quite sensitive to irradiation and may be cured in a simple manner. If there is recurrence, and this should be determined by careful, frequent, and early follow-up examinations, then the only course is radical excision, either as an anterior exenteration, removing the bladder and vagina, or a posterior exenteration removing vagina and rectum, combined in either instance with excision of the uterus and, as a rule, the ovaries. This decision remains a difficult one in gynecological therapy and is only aided by the rarity of its occurrence.

Adenocarcinoma of primary origin has been reported in the vaginal wall but this is of even greater rarity. It may be treated in a similar manner.

Secondary, or *metastatic carcinoma* in the vagina is more frequent, most often following carcinoma of the cervix. Metastasis in the lower vagina near the area of the hymen, outlet of the vagina, and Bartholin's gland region, is not infrequent, and these areas are to be carefully inspected on all follow-up examinations. Extension along the base of the bladder and urethra in the vaginal wall and metastasis in the lymphatics in this area are rather common. Retreatment with irradiation therapy may give extra-ordinarily good results in occasional cases, but more often it is a signal of the beginning of the end, and further therapy may be of no avail, followed by continuous decline and death. Exenteration operations may be performed in some individuals and by some properly trained surgeons.

Sarcoma of the vagina occurs in rare instances as the round cell type, the spindle cell type, or as the rhabdomyosarcoma. These indurated and infiltrating tumors are of great rarity, and probably are better treated by radical excision.

Sarcoma botryoides occurs in the upper vagina or cervix or both. It is a polypoid, grape-like tumor filling the vagina with multiple projections which may extend out of the orifice of the vagina. Most of these rare cases have occurred in infants. The surface of the grape-like masses is covered with normal stratified squamous epithelium beneath which there are round or irregular tumor cells of embryonic character, with occasional striped muscle cells. These rare tumors are akin to the mixed mesodermal tumors occurring more frequently in the uterus in the adult.

Chorion epithelioma may make itself known first by appearing as a purplish, soft tumor mass in the vaginal wall, singular or multiple, which may ulcerate and cause hemorrhage. The diagnosis is determined by excision and microscopic study. In some instances, this proves not to be the chorioepithelioma, but the invasive hydatidiform mole or chorioma destruens, containing molar tissue and recognizable villi. The latter may be cured by complete excision.

Hypernephroma, the clear cell carcinoma of the kidney, metastasizes on occasion to the vagina, appearing as a yellowish or a pink-red firm tumor in the vaginal wall. This may be the first recognizable evidence of the disease. *Melanomas* may metastasize to the vagina on rare occasion.

LESIONS OF THE FEMALE URETHRA

The short tubular structure representing the female urethra is subject to a surprising variety of abnormalities, because of its position, delicate membranes, attached ducts and glands, developmental variations, occasional venereal diseases, changes in natural hormones, and even the stress and strain of life.

Venereal Diseases

The urethral meatus of the female may be affected by the veneral diseases, including the temporary chancre of syphilis, acute or chronic gonorrheal infection in Skene's ducts, probably the chancroid and granuloma inguinale, and particularly the ulcerative destructive lesions of venereal lymphogranuloma. Formerly, it was thought that all infections of Skene's ducts were gonorrheal in origin. While the gonococcus thrives in that environment and must be considered as a possible cause of infection in these ducts, the *Trichomonas vaginalis* is considered to be the more common offender today. The trichomonad produces minute red dots around the meatus (and vestibule also) and may produce a caruncle of reddened, edematous appearance and the chronic white discharge that may be milked from the urethra over a period of years. Shelanski and Savitz in 1939 pointed out the relationship of *T. vaginalis* to Bartholin's gland infections (with secondary invaders) and infections of Skene's ducts; more recently, in 1955, Kean has emphasized the frequent finding of *T. vaginalis* in the urethra of women. The treatment of urethral infection from this obstinate organism rarely requires direct manipulation of the urethra, caruncle, or Skene's ducts, but does necessitate persistent and prolonged anti-trichomonacidal treatment to the vagina.

The urethral syndrome of venereal lymphogranuloma, described by Gray in 1936, apparently begins as a chronic urethritis, with or without intraurethral ulceration, which may remain extremely chronic and indolent or may proceed to urethral stricture or to ulcerative destruction of the urethra; the ulceration may extend beneath the clitoris and labia or about the introitus and deeply to the sides of the rectum; elephantiasis vulvae may be associated. This disease, diagnosed by exclusion and by the positive intradermal Frei test, produces severe chronic inflammation with no specific microscopic characteristics, is seen where venereal disease is common, is quite rare in private medical practice, and is apparently decreasing in incidence. The United States Public Health Service indicates that 2,603 cases of venereal lymphogranuloma were reported in the United States in 1946, but only 875 cases in 1955. The incidence of all venereal diseases has declined over these years.

Verruca acuminata (condyloma acuminatum), or common wart about the genitalia, may occur in the urethral meatus. The extreme proliferation of squamous epithelium and numerous mitoses at times require consideration to assure the benign character of the lesion. This so-called venereal wart may be transmitted by sexual intercourse, but it may be acquired without such a social contact. It may be treated by excision, local application of podophyllin, and probably best by fulguration.

Urethral Caruncle

Prolapse of the posterior margin of the mucosa at the urethral meatus forms a urethral caruncle. It is extremely common after the menopause, but may occur in younger women, including children. Small caruncles most often cause no symptoms; large ones may produce few complaints. Slight burning discomfort, soreness, pain on urination, and dyspareunia are associated symptoms that require treatment. Occasionally the pain is severe. Infections of the urethral meatus and Skene's ducts may be causal factors. Absence of estrogenic hormone after the menopause results in atrophy of the urethral and vaginal epithelium, with increased susceptibility to irritation, inflammation, and infection. Also the lack of hormone seems to loosen the lining mucosa.

Microscopic study shows that the true caruncles may be divided into three groups, which suggest the point of origin. Twenty per cent show the surface covered by stratified squamous epithelium, and some of these may contain gland spaces lined with transitional epithelium. Forty per cent have a surface covered partly by squamous epithelium and partly by transitional epithelium. The remaining forty per cent are covered entirely by transitional epithelium. Most of the latter contain gland spaces lined with transitional epithelium, a few of which secrete increased

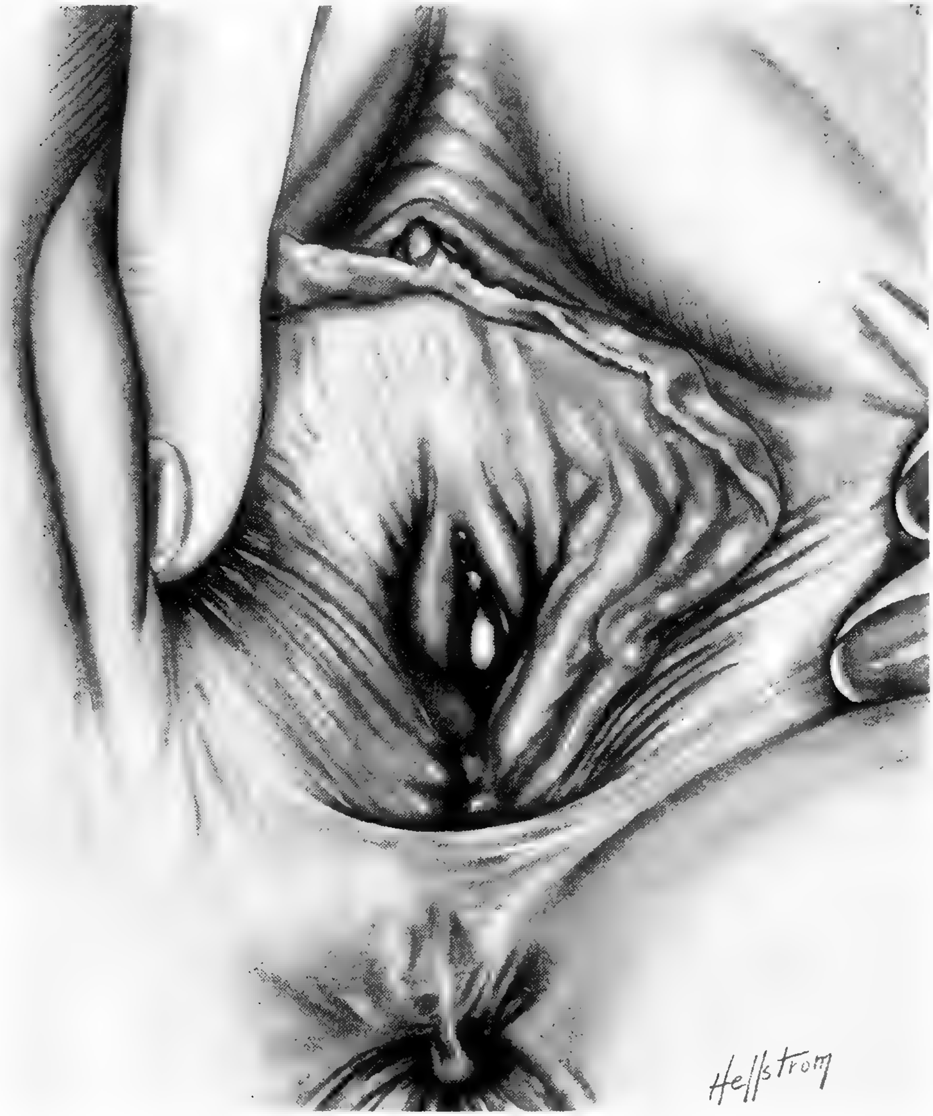


Fig. 49. Urethral caruncle. This relatively large caruncle caused pain and burning on urination, also occasionally bleeding. It represents a prolapse and oedema of the posterior margin of the urethral mucosa. Varying degrees of proliferation of epithelial cells may accompany the caruncle. On quite rare occasion, malignancy may develop.

mucus, and have a prominent superficial layer of mucous secreting cells on top of the transitional epithelium. About fifteen per cent of all cases show cellular atypia in the caruncle, mainly in the transitional epithelium. When there is much inflammation, atypical changes may be present also in the squamous epithelium. These changes, especially in the transitional epithelium, are to be carefully distinguished from carcinoma, as an error may be made in either direction. As a rule, the carcinomatous change must be very clear.

In some caruncles the blood vessels are quite prominent, which may be used to distinguish an angiomatous type. Others with extensive inflammation and very little epithelium, may be called granulomas. Some represent venereal diseases, and others have an unknown origin.

Biopsy is required in only a small percentage of caruncles. The majority need no treatment. In the case of a large or angry lesion, one showing any brittleness, hardness, or surrounding induration, one bleeding easily, or one requiring general anesthesia and fulguration, biopsy always should be performed before treatment. Often satisfactory improvement follows treatment of *T. vaginalis* infection, or the use of oral or local estrogenic therapy in older women. These are important simple treatments. Because of the great frequency of the urethral caruncle, small or large, and the rarity of carcinoma of the urethra, it appears that the ordinary caruncle represents very slight risk to the patient and that treament primarily is indicated to relieve symptoms. All caruncles are to be observed carefully at each regular pelvic examination.

Prolapse of the urethra, a circular prolapse in contrast to the more common posterior prolapse of the caruncle, occurs rarely. It may be treated by ligation around a catheter or preferably by circular excision, with resuture around the meatus.

Urethral Diverticulum

The urethral diverticulum may be of acquired or congenital origin. The acquired sac develops after perforation or local dilatation, or after infection, abscess, and rupture of a paraurethral gland. The trauma of parturition is a factor in some cases. The congenital type arises from Gartner's ducts, faulty union of primal folds, cell rests, mullerian remnant cysts, or congenital dilatation of paraurethral ducts.

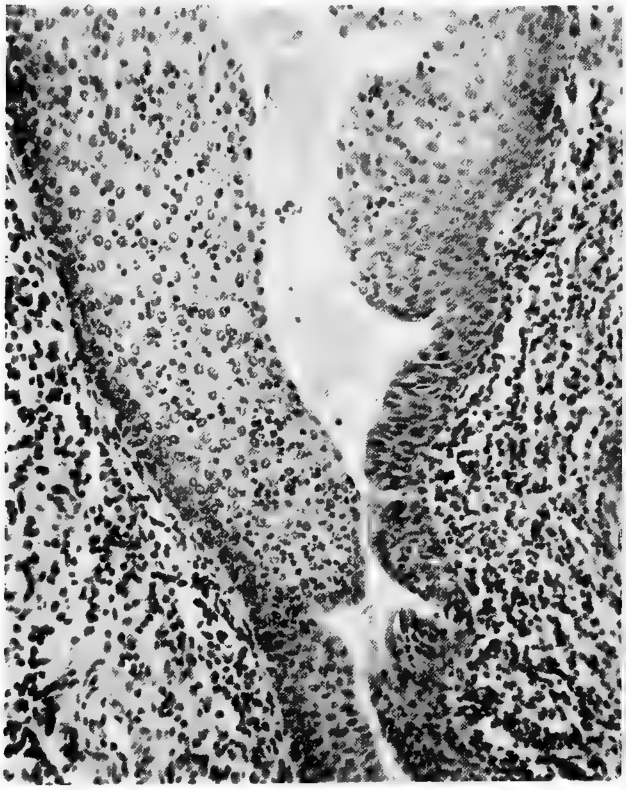


Fig. 50. Urethral caruncle showing in a crevice a partial covering with squamous epithelium, and a partial covering with typical transitional epithelium with its cuboidal epithelial surface layer. A marked inflammation is present.

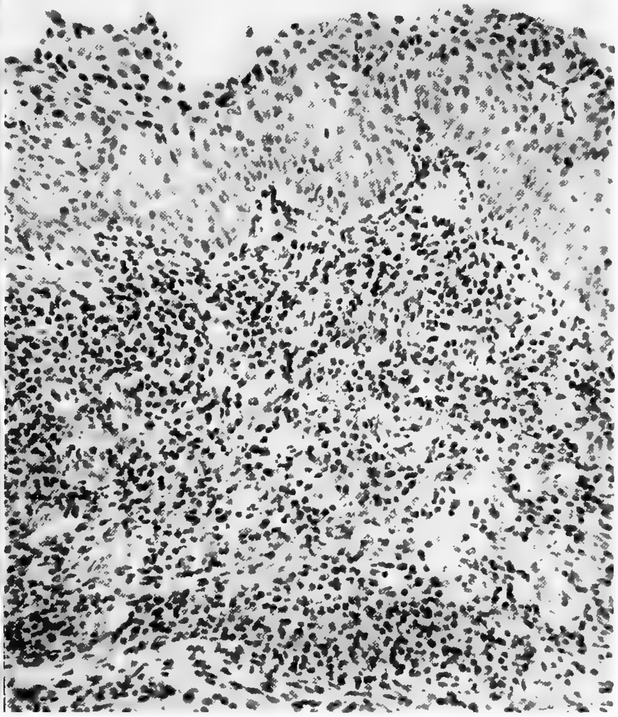
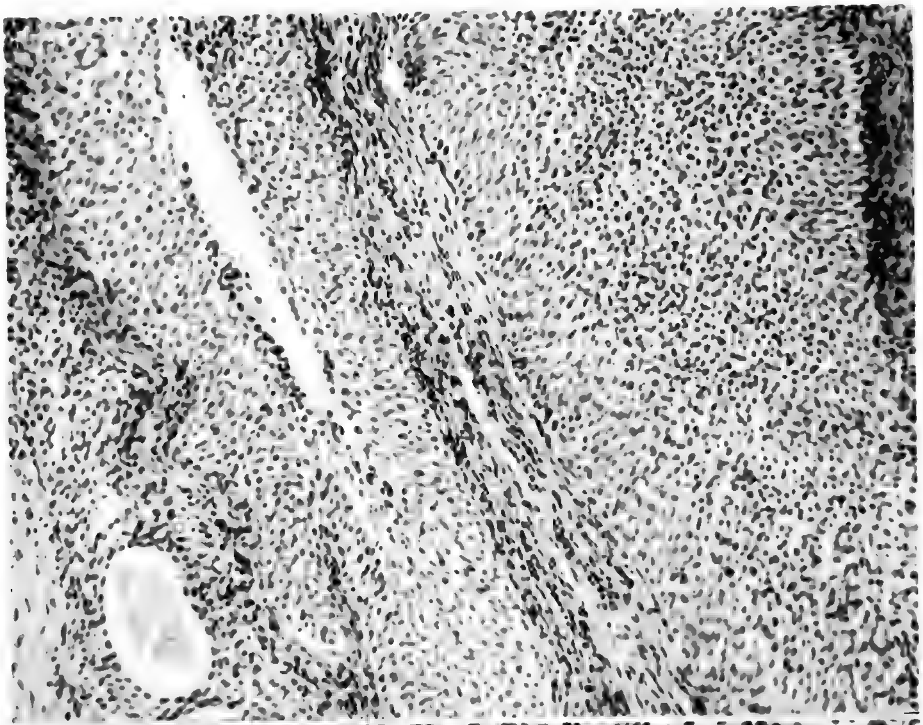


Fig. 51. Granuloma of urethral meatus or granulomatous caruncle. The squamous epithelium shows some proliferation of the basal cells into the spinal cell layer, some increase in mitoses. The severe inflammation beneath it may be related to various secondary invading organisms, or on occasion, to venereal disease.

Fig. 52. Urethral caruncle with marked hyperplasia, with transitional epithelium within its interior. Benign, though many mitoses are present.



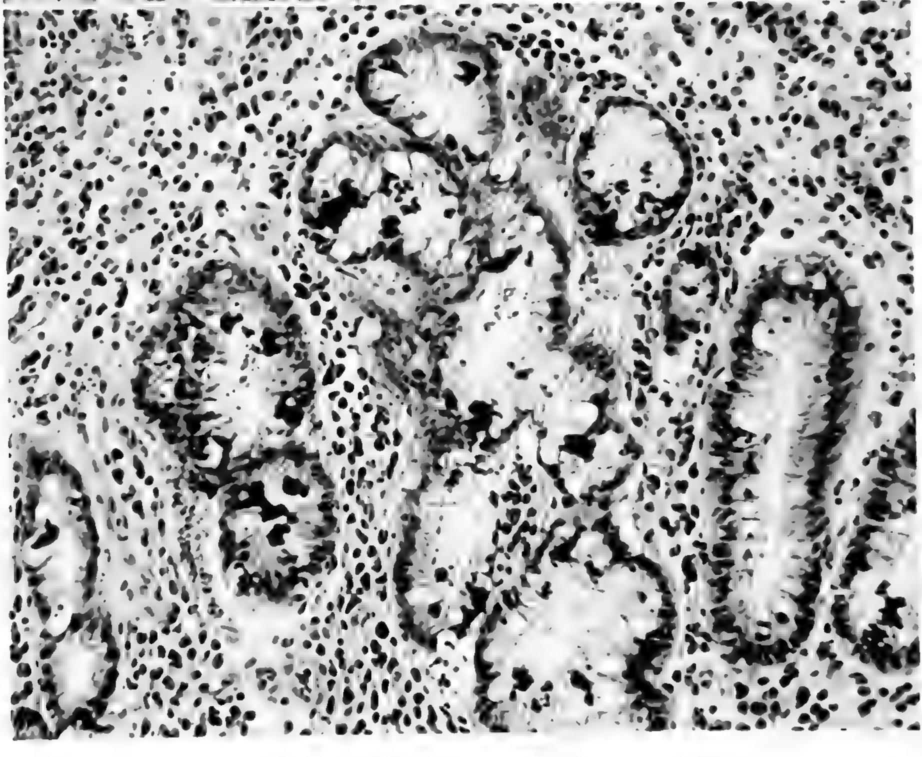


Fig. 53. Urethral caruncle with marked mucus secretion. Apparently these glands have developed from the surface of the transitional epitheliun. The formalin pigment is an artefact. A moderate inflammation is present.

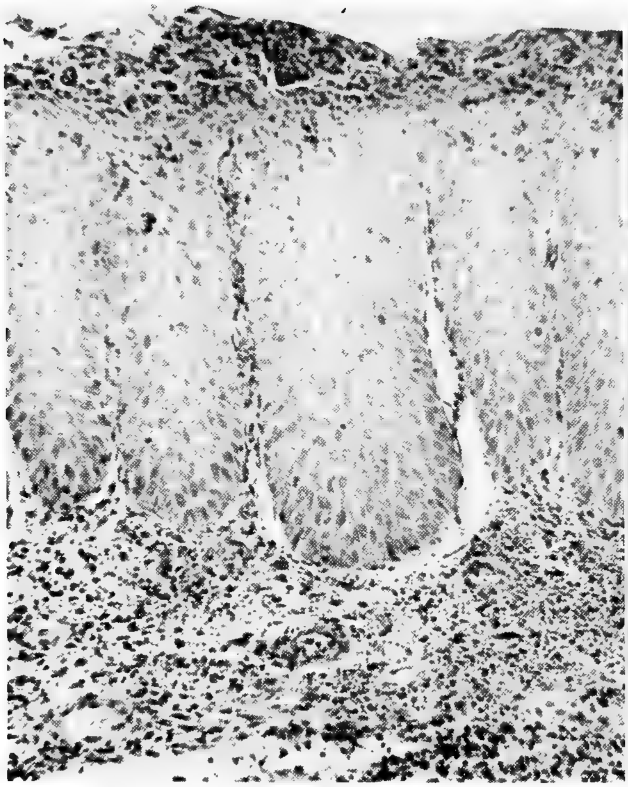


Fig. 54. Biopsy from urethral caruncle in a postmenopausal woman. The rete pegs are rather prominent, and the chronic inflammation is of moderate degree.

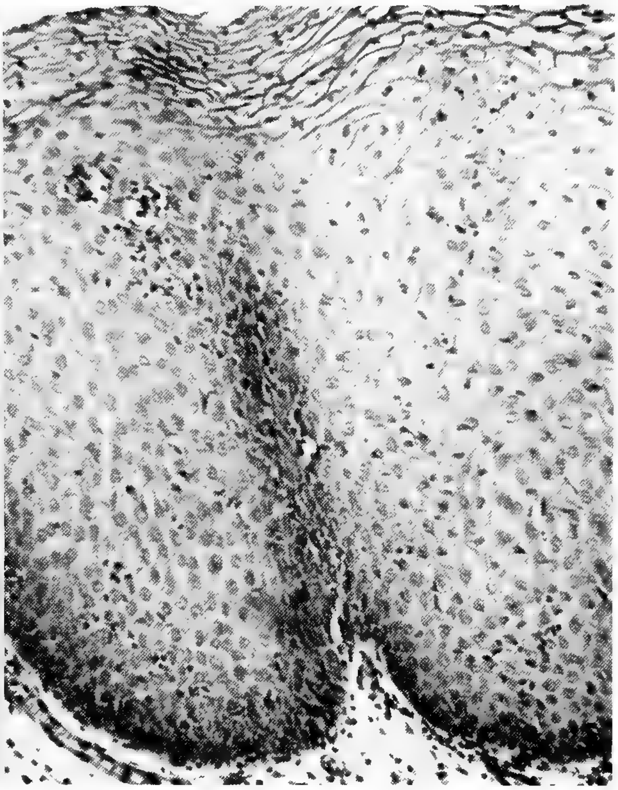


Fig. 55. Biopsy of same urethral caruncle twenty-one days after the application of estrogen cream locally every day. Note that the epithelium has become twice its thickness and that the squamous cells have become quite large and edematous. A slight inflammatory reaction persists. Grossly, there was disappearance of reddness of the caruncle, and retraction and decrease in its size.

The urethral diverticulum may or may not have the muscular layers of the urethra about it and may be lined by stratified squamous epithelium, by transitional epithelium, by a single layer of columnar epithelium, or by granulation tissue. Small tubular glands with columnar cells may extend into the wall of the diverticulum, and may resemble carcinoma, but the apparent invasion may be caused by inflammation.

In some there are no symptoms. In others there is pain in the lower abdominal, suprapubic, or perineal areas; pressure, weight, or pain in the vagina; pain radiating up into the pelvis in the sitting position; burning discomfort, severe dysuria, severe frequency of urination; recurrent cystitis, or dribbling after voiding. Pain at the end of urination and dyspareunia are frequent complaints. The diverticulum may remain undiscovered even after long investigation and treatment. The soft sac often is not palpated, but milking the urethra during vaginal examination may produce purulent fluid and prompt the diagnosis. Demonstration of the orifice at cystoscopy, whether by the direct vision endoscope or the panendoscope, may be difficult. Filling the sac for radiographic visualization may be unsatisfactory.

Complications include infection with abscess formation, which may require incision and drainage. Calculi form occasionally. Three cases of malignancy — an epithelioma, a mucous-secreting adenocarcinoma, and a

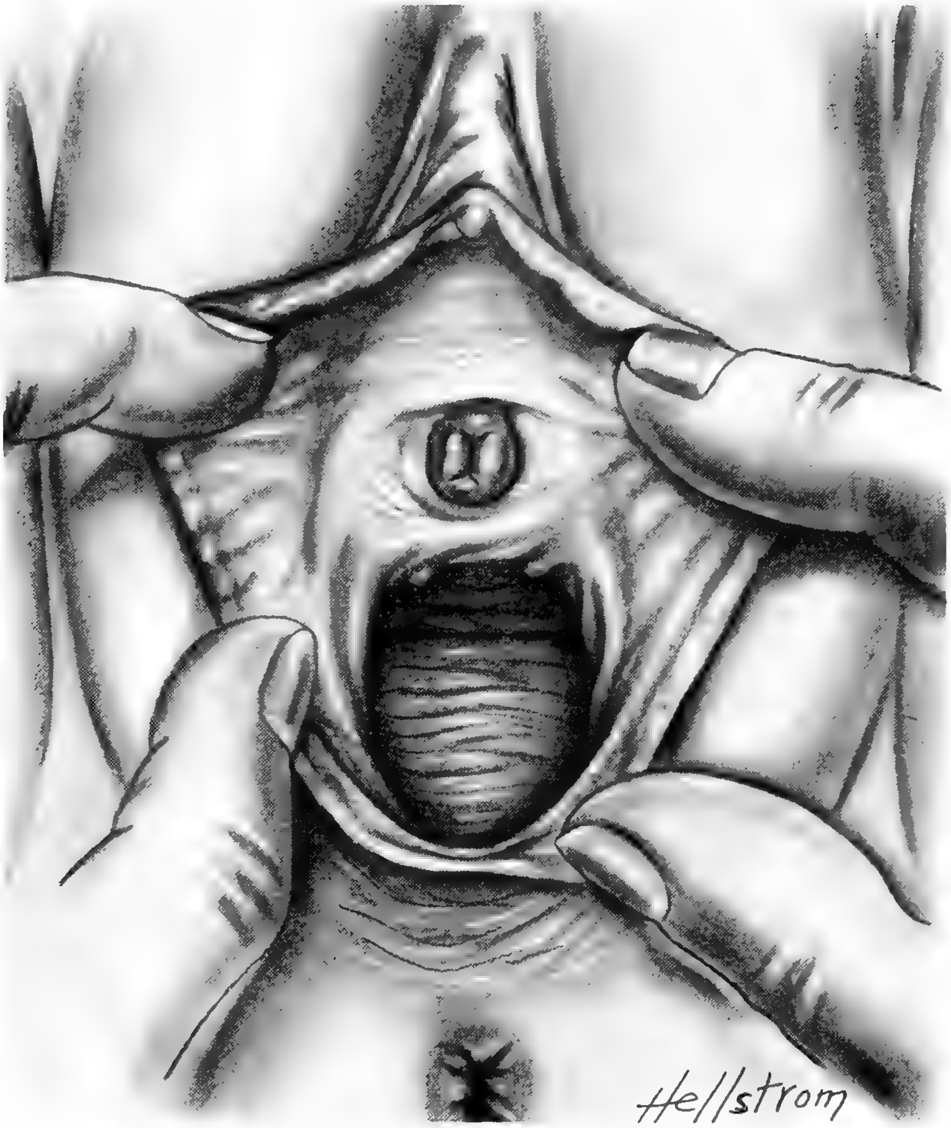


Fig. 56. Prolapse of urethra. Entire circumference of mucosa has prolapsed. If symptomatic, may be treated by excision and suture of the urethra to the margins of the vestibule. In postmenopausal women, if not severe, may be improved by estrogen cream applied locally.

transitional cell carcinoma — have been reported in three studies (Walters and Thiessen, Hamilton and Leach, and Wishard and Nourse).

Diverticula should be excised because of proximity of the infected sac to the bladder, and for relief of symptoms. Various methods have been suggested, including incising the meatus down the urethra into the sac, with subsequent excision and repair (Edwards and Beebe). Meticulous excision of the sac itself, with closure in layers, using 0000 absorbable surgical sutures in the mucosa, use of the retention catheter for ten days, and antibiotic therapy, have given good results in most instances. Postoperative complications may include fistula, stricture, or recurrence.

Suburethral Cyst

The suburethral cyst is found less commonly than the diverticulum. It may arise from a diverticulum with sealed neck, but

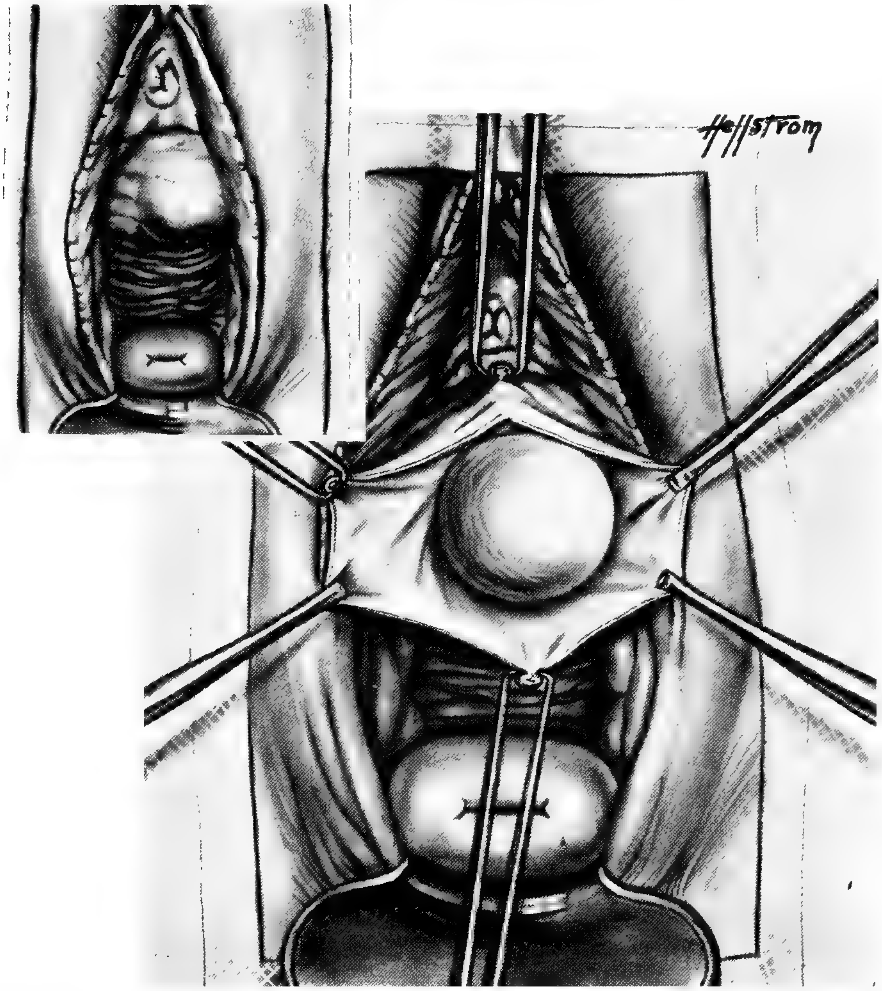


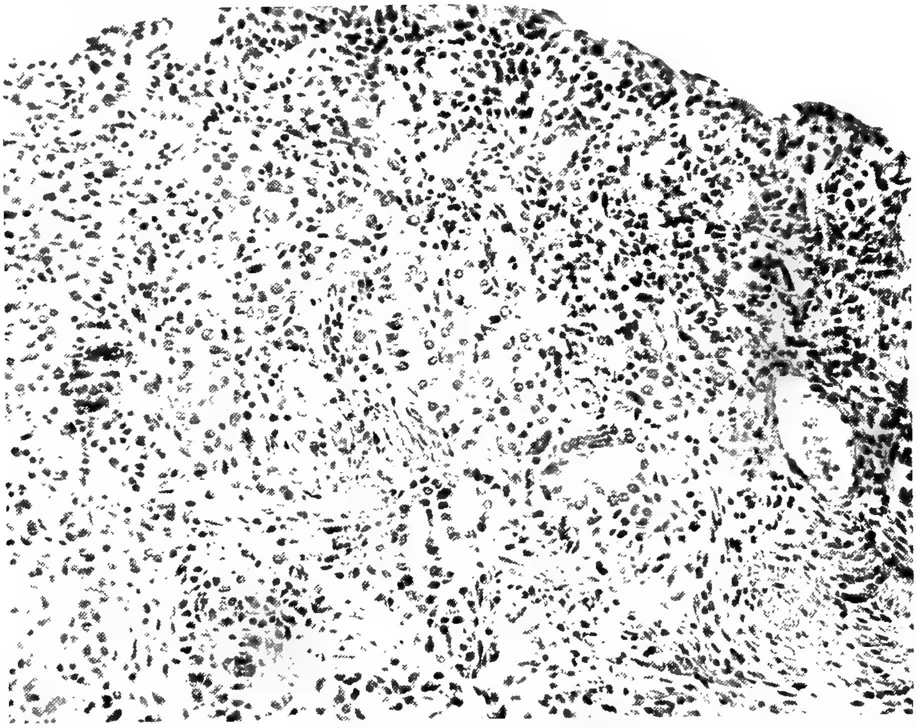
Fig. 57. Suburethral diverticulum. Excision after mobilization. The small opening in the urethra is closed with fine chromic cat-gut suture, reinforced by sutures in the pubocervical fascia, after which the vagina is closed. A Foley catheter is left in the bladder for 10 days.

more often it arises from Mullerian duct remnants or detached urethral glands. Occasionally the cyst causes marked discomfort, perhaps due to trauma and rapid enlargement, but usually it is asymptomatic. The cyst may extend up around the urethra on one side or the other. A similar lesion is the subvesical cyst, which may extend far up alongside the cervix and be removed with difficulty. It may have a lining epithelium of flattened transitional epithelium or columnar epithelial cells, or may be lined with transitional epithelium. Excision should be performed carefully and should be complete.

Carcinoma of the Urethra

Some six hundred cases of carcinoma of the female urethra have been reported to date. Symptoms include hematuria, severe dysuria, and swelling. Approximately half the patients give a history of chronic irritation or of caruncle treated previously. The gross appearance is that of a firm, rolled-out granular growth, or an indurated ulcer; more rarely, the entire urethra may be encircled with infiltrating tumor. Ritter described four types: exophytic squamous cell type, endophytic squamous cell type, adenocarcinoma (much less common), and rare miscellaneous

Fig. 58. Suburethral diverticulum with chronic inflammation and tubular glands in the wall. The diverticulum may be lined with transitional epithelium, as is the urethra, or with cuboidal epithelium. The presence of the glands in this case suggested possible invasion, but evidently was due to the inflammatory reaction.



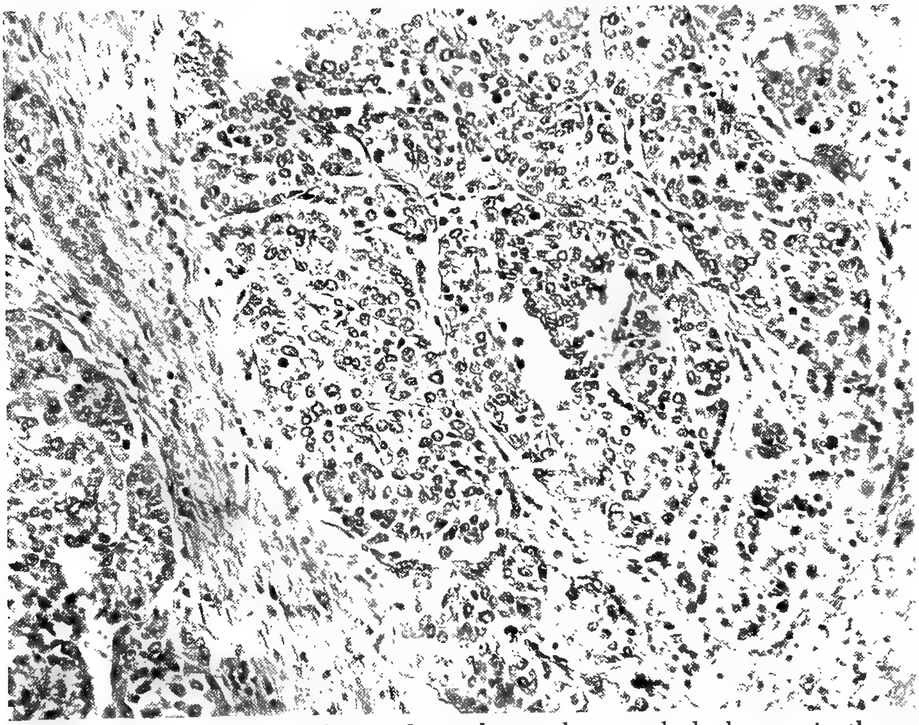


Fig. 59. Transitional cell carcinoma of the urethra, rapidly growing and rapidly fatal. The cells are fairly large, show marked changes in the nuclei and form no pearls.

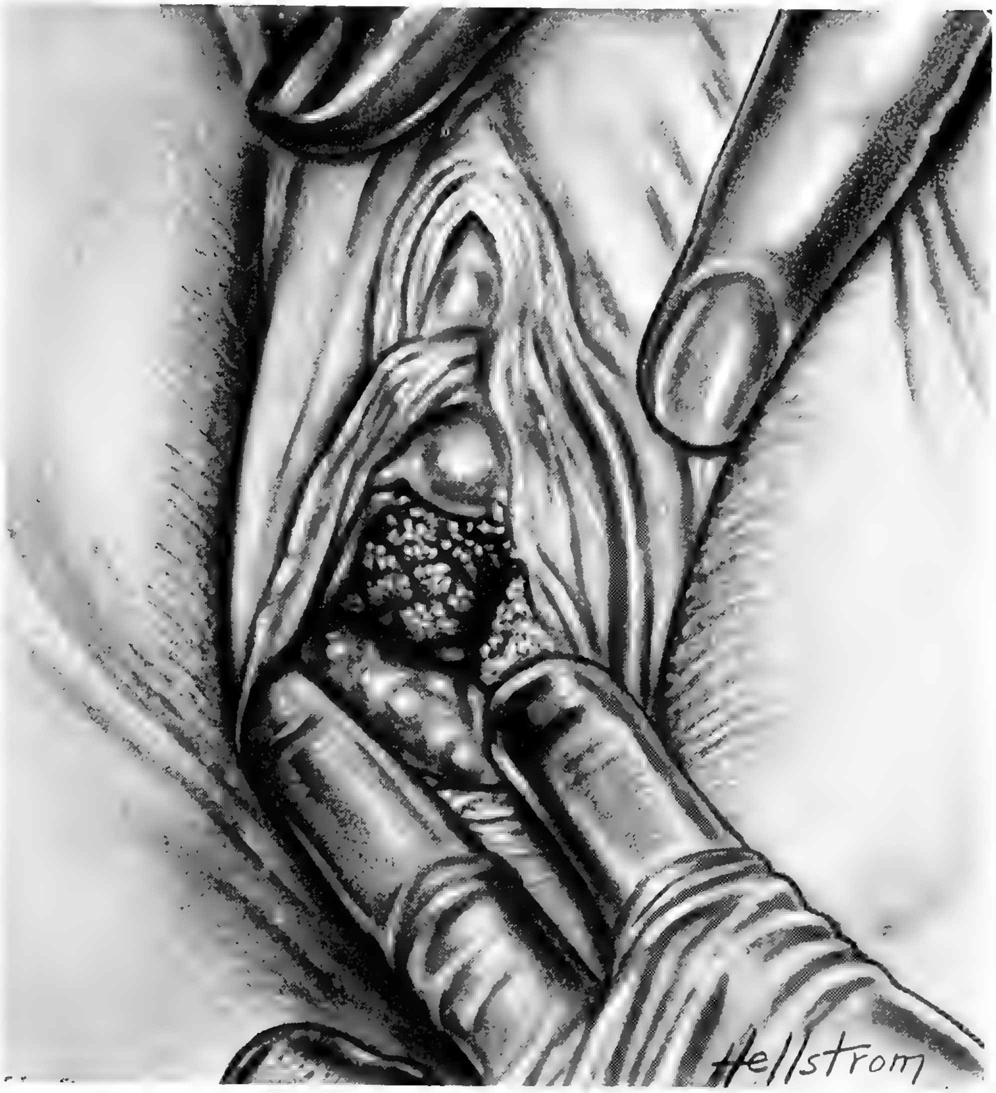


Fig. 60. Carcinoma of urethra, age 75 years. Apparently began as caruncle. Marked ulcerative destruction of urethra, with nodular, firm, granular, friable, easily-bleeding tumor.

tumors, including sarcoma and melanoma. Origin from transitional epithelium probably is more frequent than origin from squamous epithelium near the tip of the urethra. Metastases to inguinal nodes occur frequently and apparently early. Most clinicians advise operative removal with or without postoperative irradiation, but results have been discouraging. Radical excision has been tried recently. Brack and Farber reported ten cases and recommended relatively intense radium and x-ray therapy, with consideration of later excision. Removal of the inguinal lymph nodes is advisable. Most authors agree that the treatment of choice is surgical excision, but it may be that rapidly growing, anaplastic tumors should have irradiation therapy.

It seems that a slowly growing tumor with a long history may be treated better by wide excision alone, but that a rapidly growing tumor should have intensive irradiation and subsequent excision if deemed advisable. While malignancy of the female urethra is not common, early diagnosis is important.

Unusual Lesions of the Urethra

Everett and Brack recently described un-

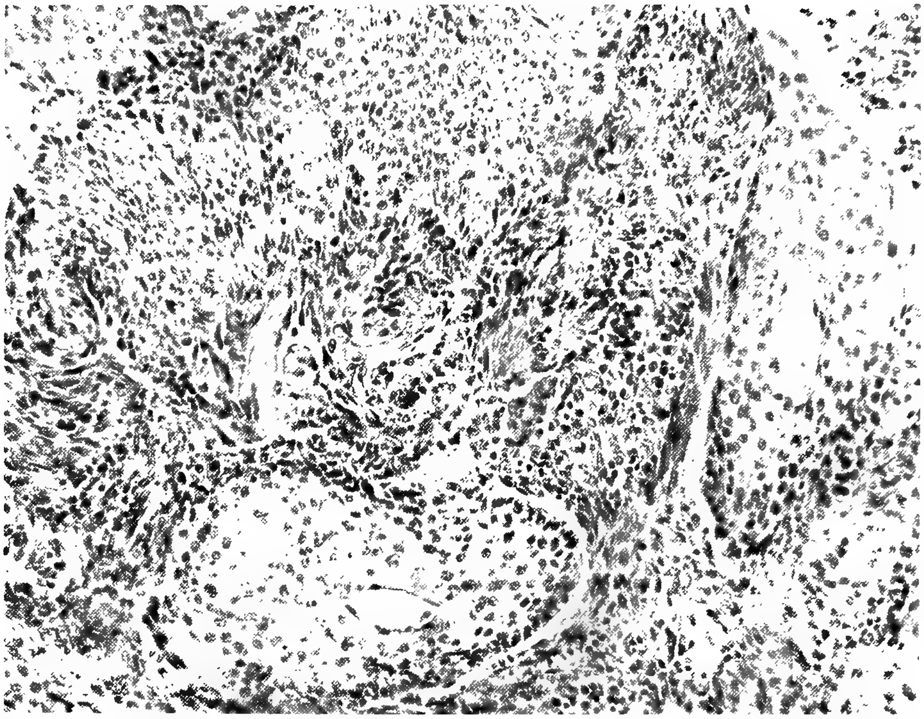


Fig. 61. Carcinoma of urethra, tending to pearl formation, more slowly growing (from case in Fig. 60).

usual lesions of the female urethra, discovered only by painstaking study with the panendoscope. These included congenital valves in children, minute urethral diverticula, and urethral polyps. The symptoms were recurring cystitis, intermittent hematuria, dysuria, and eneuresis. Schloss described caruncles of the posterior urethra and bladder neck that produced symptoms of "irritable bladder" and "chronic urethritis." These were treated by resection.

Chronic Urethritis and Trigonitis in Women

Urinary frequency, burning, and pain, in the absence of pyuria and with negative cultures, long have been attributed to chronic urethritis and trigonitis. Various treatments have included the application of dilute solutions of silver nitrate, fulguration of the bladder neck and urethra, resection of the bladder neck, dilatation of the ureters, and, most popular of all, repeated dilatation of the urethra. Numerous antiseptics have been used locally. Allergic phenomena have been implicated as a common cause by some authors (Powell and Powell).

The syndrome occurs mainly in those with great nervous tension and severe anxieties. It is remarkable how often a single severe emotional jolt seems to have precipitated these difficulties. Resolving a personal problem (unfortunately frequently impossible), reassurance, and use of tranquilizing drugs seem of more value than local urologic treatments. The results after dilatations and local therapy are rather limited.

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CHAPTER V

The Uterine Cervix

DEVELOPMENT — EVERSION

The cervix uteri in the fetus is the larger portion of the uterus. In the infant after birth and in the first few years of life, the cervix continues to make up a prominent portion of the uterus, usually more than one-half of its length. As puberty appears, the corpus of the uterus grows more rapidly and becomes the more prominent part. In the adolescent, this change continues; in the adult woman, the corpus of the uterus normally is four to six times the length of the cervix.

Microscopic changes in the cervix uteri vary with these epochs in the life of the female, and are of great interest and importance in our understanding of disease of the cervix. Robert Meyer, and others, have pointed out that in the fetus, the portio vaginalis, the external covering of the cervix made up of stratified squamous epithelium, extends far up into the cervix. Apparently this is maximal at the sixth month of fetal life. As these elements of squamous epithelium grow, the columnar epithelium begins to secrete its alkaline mucus. These secretions appear around the eighth and ninth months of intrauterine life, after which, the squamous epithelium retreats down toward the os and even out onto the vaginal portion of the cervix. Ordinarily, one would think of this retreat as extending only to the external os of the cervix, which produces the normal junction of squamous and columnar epithelium.

In this fetal development, the recession of squamous epithelium towards the cervical os is believed to leave behind a few nests of squamous cells, which may persist into adult life. Small groups of squamous-like cells may be seen beneath the columnar cells in the endocervix; these may be remains of the early squamous epithelium. These apparent vestiges of squamous epithelium are called "reserve cells." In recent years, it has been suggested that these cells may account for the origin of the squamous-like cells in squamous metaplasia, and the origin of carcinoma-in-situ up in the endocervix, perhaps also the main source of origin of epidermoid carcinoma of the cervix.

In many newborn infant girls, the columnar epithelium extends out onto the vaginal portion of the cervix, in varying degree, so as to produce an eversion of the cervix. Before inflammation, ulceration, and attempts at repair appear, the eversion has a perfect circular arrangement around the cervical os, the edges being very sharp and clear, which represents the junction of the squamous with the columnar epithelium. The single layer of the columnar epithelium allows the capillaries from beneath it to show through, producing a red appearance, whereas stratified squamous epithelium, especially where it contains glycogen, has a semi-translucent appearance, allowing much less of the color of the red cells from the subepithelial capillaries to project through this epithelium.

At birth, the stratified squamous epithelium has fifteen to twenty layers, almost that of the adult vagina, because of the strong growth effect from the estrogen of the placenta; the appearance of eversion may be very obvious at this time. As the mother's estrogen disappears from the newborn's blood in the course of two weeks, marked atrophy of the stratified squamous epithelium appears, so that after two to six weeks, the epithelium is only four to eight layers thick, contains no glycogen (produced in the epithelium by the estrogen), and the capillaries beneath this thinner epithelium are seen much more readily, which gives the vagina a pinker or more red color. Eversion of the cervix then is observed much less clearly. It is possible that the columnar epithelium regresses or retracts back into the canal of the cervix from infancy up to puberty. Information on this point is not clear. If one observes the vagina of the prepubescent child, it always has a pink or reddened appearance, due to the thinness of the squamous epithelium; and if one inspects the cervix through the Kelly cystoscope, it is difficult to determine whether the columnar epithelium is everted, or whether one is simply seeing the thin squamous epithelium. At times, it is clear that an eversion is present.

As puberty approaches, which means a few months or even two or three years before the onset of menses, and this is quite variable from one individual to another, the child's ovaries (and perhaps the adrenals too) begin to secrete estrogenic hormone. The vaginal epithelium, being most responsive, thickens, develops a grey appearance, and the inflammation that is present in all prepubertal vaginas in some degree is healed over by the new epithelium. The external portion of the cervix has precisely the same changes, with increases in layers, cornification, and the presence of glycogen. Certainly, with the approach of puberty, and immediately thereafter, one notices eversion of the cervical os in a large percentage of girls. The estrogen stimulation from the child's developing ovaries causes increased alkaline secretion of the endocervical cells, which may press the squamous epithelium back onto the portio vaginalis, and allow the columnar epithelium to grow out from the cervical os. Or, perhaps this eversion has been there since birth, and is only noted so clearly because of the great contrast in the single layer of columnar epithelium with its bright red cast and the grey translucent appearance of the estrogenically stimulated epithelium.

At any rate, these eversions are present in a large percentage of young women — perhaps fifty or even eighty per cent. Eversion of the cervix is seen extremely frequently in routine premarital examination of teen-age girls. It is likely that the condition progresses after puberty, since it appears more obvious, and more severe than in the prepubertal cervix. Very possibly the eversion is related directly to the level of the estrogenic hormone.

This eversion of the cervix, and its great frequency, is an important factor in cervical infection and abnormal epithelial reactions in a very large percentage of women. It continues throughout a woman's life, becoming more marked during pregnancy. The eversion then may appear more exuberant and sponge-like in its appearance, secrete much mucus, and later either regress to its previous state or become much worse. After the menopause, when the ovaries have ceased to function, the portio vaginalis becomes thin again, with five to eight layers of cells and loss of glycogen, allowing the underlying capillaries to become more apparent. Eversion occurs less frequently after the menopause, because the cervix becomes atrophic. But the degree of eversion does seem less than the degree of atrophy of the cervix itself, which suggests that the loss of estrogenic hormone causes the columnar epithelium to secrete less mucus, and to allow the squamous epithelium to procede nearer to the external os of the cervix. There are many gaps in our knowledge of the events marking the relation and antagonism of the columnar epithelium and the stratified squamous epithelium of the cervix.

Eversion of the cervix in the prepubertal child is rarely recognized, and apparently does not cause excessive secretion of mucus. After puberty, when the cervix is growing the eversion tends to become more marked, the degree of mucus secreted is more abundant, and it often becomes a source of annoyance to the patient. Excessive secretion may continue in the adult woman who has eversion of the cervix. While some do not complain, others emphasize the discharge. In fact, many women who come to the physician because of a vaginal discharge or leucorrhea have no infection present, but only an eversion of the cervix with an excess secretion of mucus from the columnar epithelial cells, particularly those covering the everted surface. Some women may note excess mucus in the absence of eversion, evidently due to excess secretion from the cells higher in the canal, but as a rule this is less likely to cause complaints than when eversion is present. The symptom of vaginal discharge may be just as annoying to the patient with eversion as to the patient with discharge from infection and inflammation in the cervix. The eversion may be relieved by cauterizing the cervix, which destroys the columnar epithelium. After this burned tissue has sloughed away, the stratified squamous epithelium rapidly grows over the raw area up to the uninvolved columnar epithelium, near the cervical os, or at the point where the cauterization ceased. It is most interesting that the columnar epithelium ordinarily does not tend to grow out over this burned area, certainly not to the same degree as the squamous epithelium.

Doctor Thomas S. Cullen used to tell us that treatment of eversions with silver nitrate was always followed by recurrence of the cherry-red spot. More recent reports indicate that silver nitrate may be effective, if applied liberally and frequently enough to destroy the columnar epithelium, just as does cauterization with heat. Formerly it was thought that eversion was of no importance, but today all eversions are carefully studied for accurate diagnosis and are treated when there is a complaint of excessive discharge.

ACUTE CERVICITIS

Acute inflammation of the cervix is typified in acute gonococcal cervicitis. With the onset of this acute disease, when it is still local in the cervix, there appears a profuse yellow, yellowish-white, or watery discharge from the cervix, containing numerous polymorphonuclear leukocytes. Inspection shows that the cervix is edematous, reddened, obviously acutely inflamed, sometimes slightly bluish in color, with degrees of soft, puffy eversion extending out from the os. At times, a yellowish-white exudate seems to cover the entire cervix. This inflammation may occur without pain, backache or any discomfort; the patient knows she has a very abnormal discharge. Smears from the cervix stained with Gram's stain contain the typical gram-negative intracellular diplococci. The organism grows readily on chocolate agar media cultured in "candle-jars" (micro-aerophilia). Ordinarily this acute inflammation is severe, but at times it may be less obvious and may be overlooked. The infection should be treated by one of the antibiotics. Local therapy is unnecessary. The patient should be warned about spread by contact. The reader is reminded also of the need for treating the male partner.

There are other causes of acute cervicitis, including chemical causes. The trichomonas vaginalis, when it forms an acute vaginitis with yellowish-white foamy discharge, not infrequently causes the cervix to be extremely reddened, edematous, and to appear to have a rather marked erosion or eversion about the cervical os. Treatment with trichomonacides may allow the cervix to return to a more normal size, with loss of the edema and with healing of the erosion, so that it may return to the pale pink color. Perhaps the streptococcus, the pneumococcus, and even the diphtheria bacillus may cause acute cervicitis, but one rarely distinguishes such forms of inflammation of the cervix on clinical grounds.

CHRONIC CERVICITIS

Chronic "eversive" cervicitis, frequently called "erosion" of the cervix, or chronic cervicitis, is the most frequent infection in the pelvic organs of women. The first term recently has been re-emphasized by Barnes and Allen, and it seems to be appropriate. The older term of "erosion" of the cervix suggests a raw, denuded ulcer about the cervical os, and certainly it does look like a raw ulcer to the naked eye. However, on biopsy the surface is covered by a single layer of columnar epithelium, at times by squamous metaplasia, by dysplastic epithelium, or even by areas of carcinoma-in-situ. Ulcers, or destroyed areas of squamous epithelium, are rarely seen in the microscopic specimen, evidently because healing is so rapid. Either columnar epithelium rapidly overgrows the destroyed area, or squamous epithelium quickly covers the area of destruction. Minute areas of ulceration are found at times, and these occur in conditions of severe inflammation with true ulceration.

This chronic eversive cervicitis seems to develop in the congenital or hormonally induced everson of columnar epithelium of the endocervix. Pathogenic bacteria from the vagina invade the columnar epithelium to cause

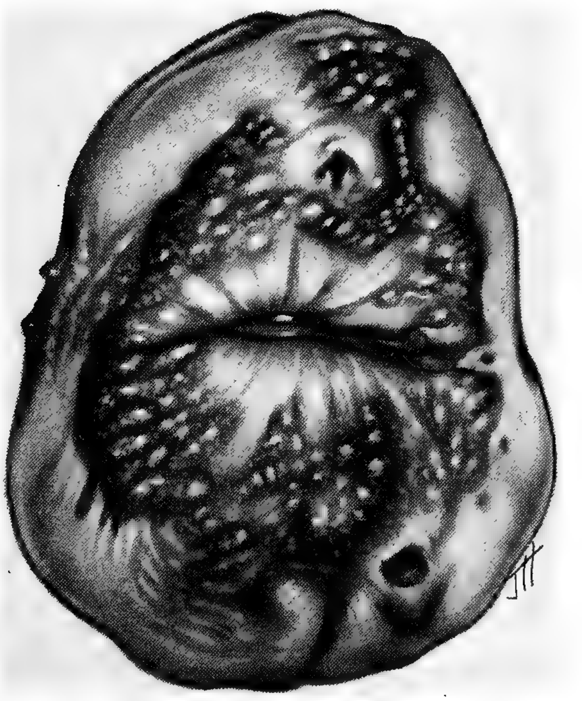


Fig. 62. Marked chronic cervicitis. The excised cervix shows marked eversion of the endocervix; the central area represents a single layer of intact columnar epithelium. Beneath, there is moderate chronic inflammatory reaction. Beyond the smooth columnar layer are the numerous irregular small slightly raised glazed, or faintly white areas, which represent the overgrowth of squamous epithelium, or undergrowth of squamous epithelium, or squamous metaplasia and scarring. These are the results of attempted healing of minute ulcerated areas. The irregular border attests to the inflammatory origin. Dysplasia, carcinoma-in-situ or invasive carcinoma may be present in any lesion similar to this.

subepithelial inflammation and areas of minute ulceration, with exudation of serum and polymorphonuclear leukocytes to form a purulent discharge. The bacteria involved are from a mixed flora and include streptococci, the colon bacillus, staphylococci, and others. The discharge is not composed of clear mucus with normal squamous epithelial cells, but of mucopurulent exudate and enmeshed bacteria. This eversive cervicitis undoubtedly occurs in the prepubertal child, but is overlooked because of the predominant character of the vaginitis. The vagina is so thin and reddened in the young child that the reddened eversion is difficult to distinguish, and the differentiation is not nearly so clear as in the adolescent or adult woman.

Some thirty years ago, Schiller in Germany advised that iodine be applied to the cervix, to distinguish the normal glycogen-containing squamous epithelium of the cervix from nonglycogen containing cells. The iodine is applied as Lugol's solution, which contains iodine 1 Gm., potassium iodide 2 Gms., and water 300 cc. This solution may be poured into the vagina or introduced against the cervix by the saturated gauze sponge. It must be applied in generous amount. After two or three minutes, the excess iodine solution is mopped away, and the cervix is carefully inspected. The vaginal walls and the portio vaginalis of the cervix, covered by normal glycogen-containing epithelium, stains a dark brown color, due to the iodine reaction with the glycogen in the cells. The eversion, if covered by only columnar epithelial cells, will take no iodine. However, the application of this stain may show areas that do take the iodine stain, evidently due to squamous epithelium in these areas. Other areas may stand out as a white plaque, not taking the iodine, yet not representing the ordinary columnar cell eversion. Such white areas may indicate carcinoma-in-situ, dysplasia, or leukoplakia.

Further studies of many cases of eversion of the cervix have shown that while ulceration occurs extremely rarely or is quickly healed over, squamous metaplasia (the growth of squamous-like cells beneath columnar cells) and the overgrowth of squamous epithelium in these areas are frequent, and dysplasia and carcinoma-in situ are found rather often in areas of eversion of the cervix. There is a constant rivalry between the squamous epithelium and the columnar epithelium to cover any denuded areas in the eversion. The squamous epithelium usually is dominant, at least in adult life. Certainly the majority of cases with chronic eversive cervicitis shows a very irregular margin about the cherry red spot, in contrast to the sharply demarcated circle when there is eversion without any inflammation, because the squamous epithelium has grown at many points into the area of eversion, in attempts at healing inflammation.

Only a few years ago, it was commonly taught that eversion or erosion would not contain cancer, unless there were obvious gross changes. Today it is well known that the "erosion" of the cervix, or chronic eversive cervicitis, may contain many abnormal changes in squamous epithelium, including dysplasia, carcinoma-in-situ, or even early invasive carcinoma of the cervix.

Hinselmann perfected the colposcope, a magnifying telescope for inspecting the cervix under fifteen or twenty power magnification. He and his many followers, including today such outstanding Continental gynecologists as Navratil, believe that inspection of the cervix with chronic eversive cervicitis may allow one to distinguish areas of carcinoma-in-situ, or early carcinoma. At least, they believe that the colposcope is a great aid in *selective* biopsy of those areas that may represent abnormal changes. Navratil speaks of this eversion, or chronic eversive cervicitis, as "erythroplakia," the red spot or red plaque. He believes that the combined use of the Papanicolaou cytology technique and selective biopsy by means of the colposcope aids the discovery of the greatest percentage of early carcinomas of the cervix. Undoubtedly, selective biopsy is an important aid to diagnosis, but recent reports indicate that the carcinoma-in-situ may arise high in the cervix, beyond the view of any colposcope, in perhaps half of the cases. If this is true, then cytology is the best single routine method for discovering those lesions. Smears or biopsy, or both, should be routine before any treatment, especially destructive treatment, as cauterization, is undertaken.

Chronic eversive cervicitis may be treated by antibiotics with some degree of improvement, and some gynecologists feel this is the most important method; it may be treated by the Hyam's conization, using the electric wire with cutting current to remove a cone of tissue about the cervical os, though this method may be followed rather frequently by stricture of the cervix; one may remove all of the raw appearing areas by numerous biopsies (Thomas); one may use radial cauterization of the cervix, as suggested many years ago by Hunner and others; or, one may sear the cervix with the flat blade of an electric cautery, destroying all the columnar epithelium and such partly regenerated squamous epithelium as may be present, although this may be followed by stricture about the cervical os. It must be realized that all forms of cauterization have their drawbacks and may be followed by varying degrees of stricture formation. This author follows the radial cauterization method, with perhaps light searing between the radial strokes. When cytology studies are suspicious of malignancy, the sharp conization for further examination of the tissues is followed by excellent healing without stricture formation and makes an excellent therapy for chronic eversive cervicitis.

CHRONIC CYSTIC CERVICITIS

A frequent form of chronic cervicitis is chronic cystic cervicitis, in which one, several or numerous small cysts are seen and felt projecting from the cervix around the os. These cysts ordinarily are quite small, three or four mm. in diameter, but occasionally single cysts may become enlarged to two or three cm. in diameter. Such a large size is unusual. Cysts in the cervix are produced by obstruction of the ducts of the endocervical glands, usually caused by inflammation, occasionally by stenosis due to metaplasia. The inflammation ordinarily is of very minor degree, or perhaps it was of more marked degree at an earlier stage. The scar tissue around the ducts of the endocervical glands later constricts the glands, with subsequent accumulation of mucus and formation of cystic dilatations or minute mucoceles. The presence of small cysts rather far out from the cervical os (two or three cm.), suggests a previous extensive eversion, which may have been healed over by normal squamous epithelium, entraping small cervical glands, later forming the small cysts. As a rule, the tissue sections show extremely little active inflammation; and these cysts are of no real importance since they harbor no active infection.

When the patient learns that she has cysts of the cervix, much concern often is produced. The term "cyst" has serious connotations to the laity, and it may be difficult to dispel their fears. Multiple small Nabothian cysts of the cervix really need no treatment, but, because of their presence, more often they are treated by radial cauterization of the cervix or individual cauterization of the prominent cyst or cysts, which opens them, allowing the mucus to drain out into the vagina. This is followed by healing and disappearance of the cyst. Evidently scar tissue must obliterate the cyst, so that it does not reform.

These cystic changes in the cervix may occur up in the canal, up to the junction with the endometrium. These may not be diagnosed, because they cannot be seen or felt.

Ordinarily, chronic cystic cervicitis is relatively unimportant, although routine and regular survey of these cervices is not to be discounted.

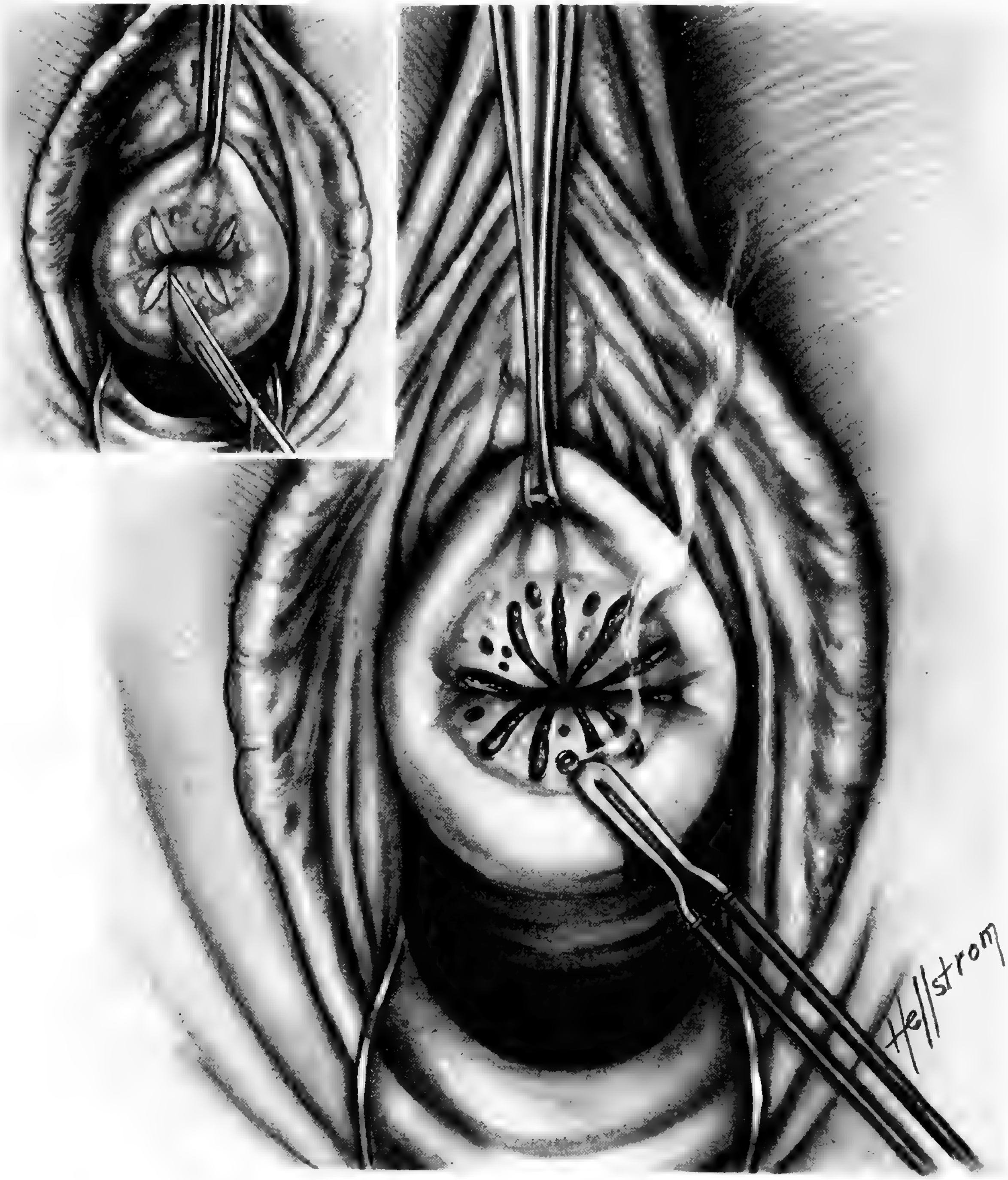


Fig. 63. Biopsy and radial cauterization. Four quadrant or more biopsies may be taken in the office with various punch biopsy instruments. Here the patient is having biopsy and cauterization under anesthesia. The scalpel excises wedges of cervix, extending well up into the endocervix and outward beyond the squamo-columnar junction. Radial cauterization was emphasized to the profession by Guy L. Hunner, fifty years ago, and remains one of the best treatments. This patient has had negative Papanicolaou smears. Usually curettage of the endometrium accompanies this operation.

ENDOCERVICITIS

Chronic endocervicitis, when used as a specific term, means inflammation of endocervical glands, with purulent discharge, without obvious external cervicitis, without eversive cervicitis or the formation of visible cysts. Endocervicitis alone is less frequent

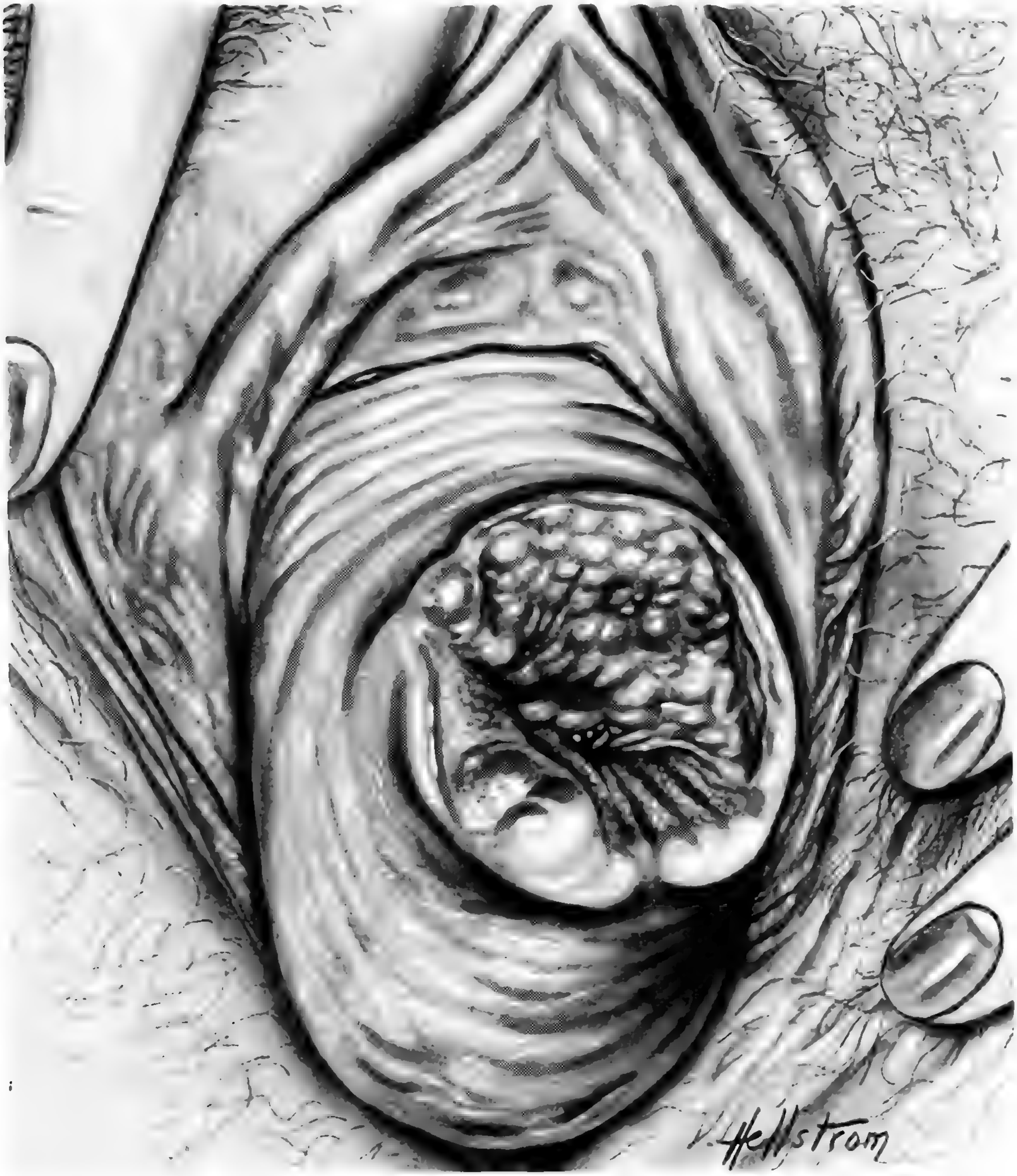


Fig. 64. Marked chronic cervicitis in patient with complete prolapse of the uterus. The lacerations, eversions and Nabothian follicle cysts are evident. Rarely is carcinoma associated with complete prolapse, but always it must be excluded. This complete prolapse (procidentia) has an associated enterocele, bulging behind the cervix.

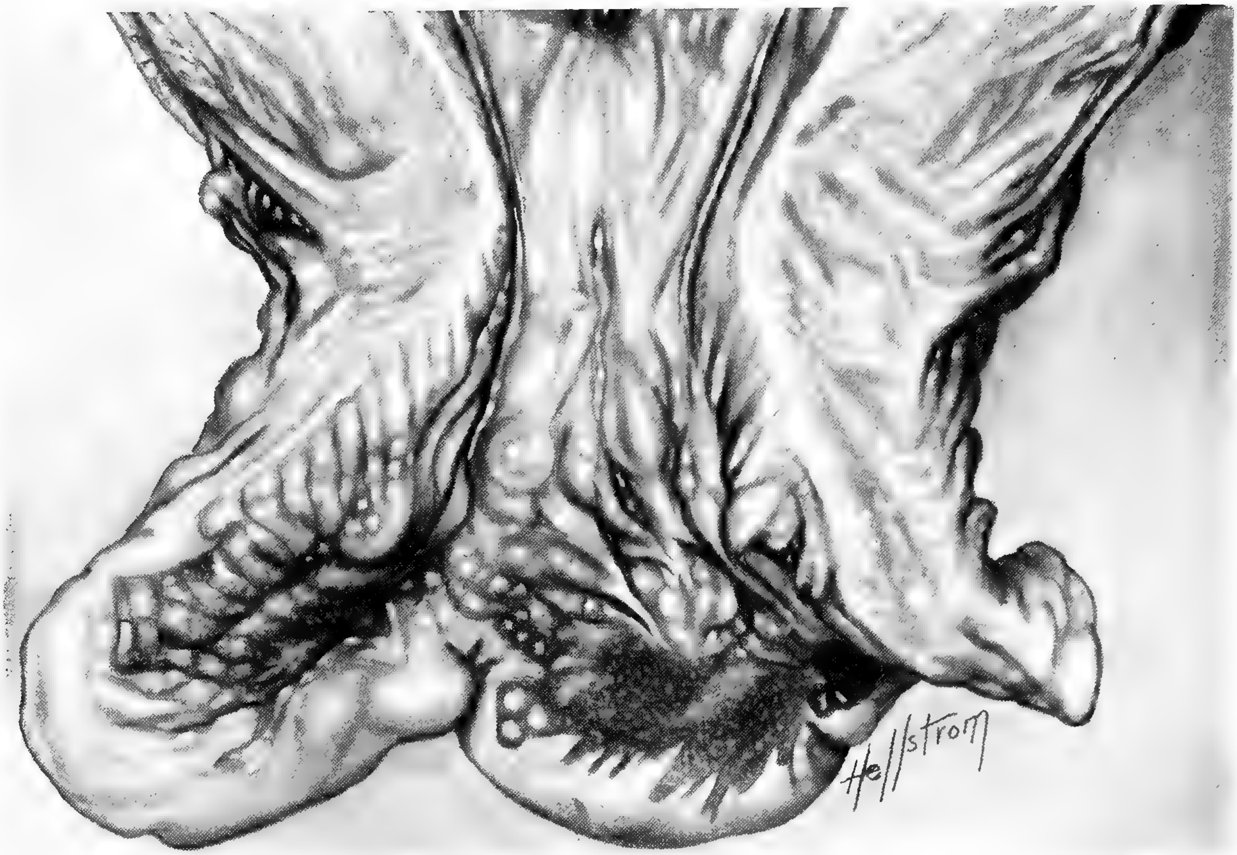


Fig. 65. Tuberculosis of the cervix, diagnosed only by microscopic study. This appears no different from an ordinary chronic eversive cervicitis with multiple lacerations. Some Nabothian follicle cysts are present rather high in the endocervix. This patient also had tuberculosis of the endometrium and fallopian tubes, not diagnosed preoperatively.

than eversive cervicitis, but it always accompanies eversive cervicitis in varying degree. Patients with this entity complain of a thick, purulent discharge which appears as a yellowish or gray mucus plug in the cervix at the time of examination. The presence of pus cells in the secretion points to the presence of endocervicitis, if the vagina and external cervix appear grossly normal. Various bacteria, including streptococci, staphylococci, and coliform organisms, may produce a slight, moderate or marked infiltration with polymorphonuclear leukocytes, lymphocytes and plasma cells, surrounding the endocervical glands.

Treatment has included dilatation of the cervix, and some gynecologists claim that dilating the canal to allow better drainage is a most important factor. It is difficult to see how this helps to drain the individual glands. Repeated dilatations in the office have been advised. In other instances, under pentothal anesthesia, the cervix may be dilated widely and be cauterized high in the canal with radial strokes of the electric cautery. Some use Hyam's conization, removing a cone of tissue extending far up into the endocervix. The Sturmdorf amputation is advocated in some circumstances. Cauterization of the endocervix unfortunately produces more strictures than external cauterization, and electrical conization is even more apt to do so, with disconcerting sequellae. In recent years the tendency is to culture the cervical mucus, isolate the organisms present and determine their sensitivity to the various antibiotics, so that appropriate antibiotic therapy may be administered parenterally or orally. This is a logical procedure. A few gynecologists advise the use of antibiotics for eversive cervicitis, but most agree that mechanical destruction of the latter lesion is necessary for cure.

LACERATED CERVIX, ECTROPION

Most cervices are lacerated during vaginal deliveries, in many small areas at least, and sizeable lacerations are not infrequent. Often the obstetrician will find and suture the fresh lacerations, if these are fairly large. Sometimes they are overlooked or not repaired promptly. Lacerations of the cervix, or tears, may seem rather marked at delivery, but become so small after two or three months, as to be hardly noticeable. But deep tears, extending well into the wall of the cervix, or into the vaginal fornix, are very obvious at all future examinations. The laceration may be single on one or the other side, most frequently at three or nine o'clock, but there may be multiple lacerations at varying points around the circumference of the cervix. The tear or tears allow the endocervical mucosa to be everted against the vaginal surfaces. This red and raw appearing eversion may be unaccompanied by inflammation, but may produce an excessive clear mucus discharge. More often there are varying degrees of inflammation, with exudation of lymphocytes, plasma cells and some polymorphonuclear leukocytes beneath the largely intact columnar epithelial cells of the everted endocervix. This inflammation may be marked and is commonly described by the term "ectropion." Sometimes the laceration is so deep, especially when in one lateral fornix, as to cause concern for the safety and welfare of the mother in subsequent pregnancies, because extension of the tear might involve the large uterine vessels and even the bladder and ureter. Deep lacerations may result in subsequent miscarriage, especially during the sixth or seventh month of pregnancy; but it is surprising how often subsequent delivery occurs without any complications even though the tear was unusually deep. This does not imply that cervical lacerations may be dismissed as of no great consequence.

An inflamed, lacerated, everted cervix must be examined carefully, because there are more surfaces available for the beginning of malignant growths. Prophylactic measures include cytologic examination by the Papanicolaou technique and the Schiller (iodine) test. Colposcopic study undoubtedly is of value to those who have trained themselves in its use. Biopsy of various areas is an essential diagnostic procedure. If the lesion is benign as judged by these studies, the cervix may be treated by radial cauterization, to produce retraction, shrinkage, and to remove the everted endocervical epithelium, thereby allowing the squamous epithelium to grow onto the everted area. The active inflammation beneath the columnar epithelium subsides greatly, and the cervix becomes more healthy. Following complete healing by some months, one may choose to repair the cervix by denuding and approximation of the edges of the laceration with chromic sutures. Multiple lacerations may be repaired in this manner. Alternatively, the laceration may be repaired without previous cauterization. This may bring the everted endocervix back into its protected canal and allow resorption of much of the inflammation (especially when supplemented with antibiotic therapy). If cauterization of the cervix does not sufficiently alleviate the condition, trachelorrhaphy may be performed at a later date.

Amputation of the cervix by either the Sturmdorf method or the Schroeder guillotine method may be performed if the laceration is extensive and the inflammation severe. Amputation is regarded with increasing disfavor, because many believe that deep cervicectomy interferes with fertility and normal progression of pregnancy. The lacerated and infected cervix is rarely an indication for hysterectomy, although it may be an indication when the infection is extra-ordinarily severe, and when it does not respond to simpler treatment. Following the lacerations, the anterior or posterior lip of the cervix may become quite elongated, especially if there is some degree of descensus of the uterus. The reason for this is not apparent. The elongation may reach such marked proportions, that one lip may appear at the vaginal orifice. If there is no other pathology, simple amputation and plastic repair of the cervix is indicated. Of the two types of amputation, the Sturmdorf type is preferable, a conical excision with suture of the vaginal mucosa into the canal. The old Schroeder amputation was of the guillotine type, abruptly excising the cervix and suturing the mucosa into the canal all the way around, as well as possible. This method results in a more irregular surface than the Sturmdorf method, which, if not too much of the cervix is excised, may produce an almost normal appearance of the reconstructed cervix.

CERVICAL STRICTURE

The most frequent cause of stricture of the cervix is some form of cauterization (including conization) or other operative procedure. Such narrowing may cause difficulty in menstruation, with dysmenorrhea, though it is strange to see how many extremely small orifices cause no pain whatever. Why some have severe pain, and others do not, is unclear. Dilatation of the cervix brings relief to many, sometimes for only a few months. All narrow annular openings in the human body tend to return to their previous small size after forcible dilatation. Perhaps the dilatations cause disruption of the nerve fibers in the cervix and relieve pain in that manner, in some instances.

Complete occlusion or sealing over of the cervical os from cauterization is more obvious. If the patient continues to menstruate, the cervical canal and even the endometrial cavity may become distended with blood. There may be marked cyclic menstrual cramps, without external bleeding. If the patient is postmenopausal, a large amount of mucus may accumulate behind the sealed cervix, especially if estrogens have been given. This causes pressure discomfort in the pelvis. As a rule, these external seals are readily removed with the cautery in the office, and usually the canal reappears normally after healing.

Stricture of the cervix with hematometrium, mucometrium, or pyometrium, occurring postmenopausally, without history of cauterization, often is associated with carcinoma of the endocervix or of the endometrium. This is especially true with pyometrium. The patient complains of pain in the pelvis, perhaps low grade fever, and has a tender enlarged uterus. If there is pyometrium, dilatation and drainage is indicated. If one can obtain some tissue for diagnosis, by very gentle curettage, the disposition of the case is simplified, but in some, thorough curettage must be performed a few weeks after drainage and improvement.

Congenital stricture of the cervix was considered a frequent and important cause of adolescent dysmenorrhea in former years, but this seems less important as we understand more of the relation to ovulation, growth of the uterus, and psychologic anxieties. In a few cases, congenital stricture must be important, and dilatation of the cervix under pentothal anesthesia may result in improvement. Again, perhaps the nerve fibers in the circular muscles of the cervix are disrupted. If partial cervical obstruction is a factor in retrograde menstruation, which is regarded as an important cause of pelvic endometriosis, then degrees of cervical stricture must be frequent. Certainly pelvic endometriosis is a frequent finding in private practice.

Narrowing of the cervical canal often is associated with acute anteflexion of the uterus, a congenital development. Dysmenorrhea of marked degree may be associated. Dilatation of the cervix and insertion of a stem pessary may alleviate the pain considerably, but this is indicated infrequently. The stem pessary, made of hard rubber or plastic, is sutured into the sides of the cervix with heavy braided silk. After six weeks, the sutures are divided, and the pessary is removed readily. Occasionally, remarkable relief follows this procedure. But the anteflexion and narrowness of the canal tend to revert to the original state, which is discouraging. Stem pessaries are used in much fewer cases in recent years.

CERVICAL POLYP

The cervical polyp occurs frequently as a protruding, soft, bulbous, edematous, pink or red, round or elongated, soft tumor, arising from the endocervical canal. Its origin is similar to that of the urethral caruncle, which is a prolapse of the lining mucosa. In the urethra the prolapse occurs chiefly in the posterior margin while in the endocervix it may arise at any point. The polyp should not be considered as a true tumor. These lesions are never seen before puberty and usually occur after the age of thirty years. Often

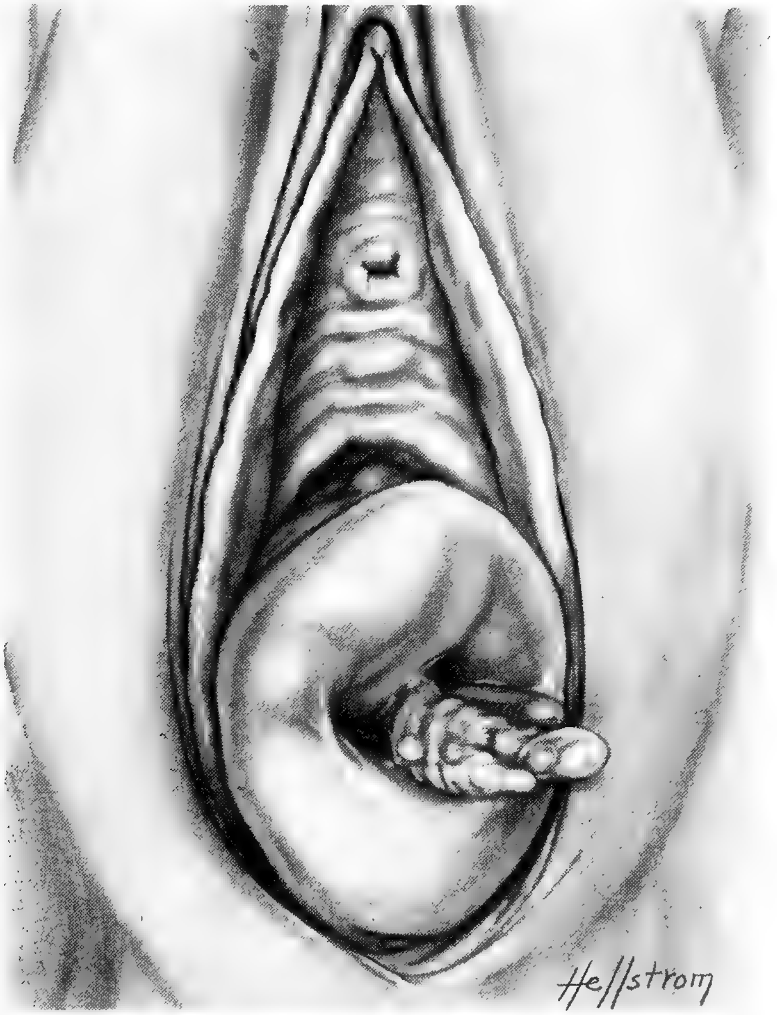


Fig. 66. Cervical polyps in patient with second degree prolapse.

they are associated with some eversive cervicitis, frequently are seen during pregnancy and not rarely are found after the menopause. The cause is unknown. One per cent of cervical polyps is malignant. While the danger of malignancy is not great, yet every polyp that is excised should have microscopic study. Years ago when the author was a resident, Doctor Guy L. Hunner had removed a beautiful cervical polyp, placed it in a small bottle of fixative and had brought it to the class of medical students. In his discussion, he remarked on the infrequency of malignancy. In the digression of teaching, this polyp was not sectioned for several weeks. It was most disturbing to find that the entire polyp represented adenocarcinoma. The patient was recalled for total hysterectomy. This dramatic exception made a deep impression of the necessity for microscopic examination. Histologic examination of a polyp usually reveals a surface covered with a single layer of columnar epithelial cells with numerous glands of typical endocervical type in its interior; portions of the polyp may be covered with stratified squamous epithelium, and sometimes the entire surface is covered with squamous epithelium. Squamous metaplasia, the growth of squamous epithelium beneath columnar epithelium, occurs frequently in cervical polyps.

Treatment of the cervical polyp is excision. If there has been no intermenstrual bleeding, and if the patient is not pregnant, the polyp may be removed in the office by clamping as high on the base as possible and twisting it away from the cervix. A large polyp with very broad base occasionally may need suturing after clamping and excision. If there is any intermenstrual bleeding, or prolonged and irregular menstruation, the patient should have curettage of the uterus, following the removal of a polyp in the operating room. A polyp which occurs after the menopause may represent a sentinel polyp, benign itself, but occasionally associated with adenocarcinoma of the endometrium. Even though there has been no postmenopausal bleeding, one should consider the advisability of performing curettage of the uterus, following removal of the polyp in the operating room. This coincidental relationship has been reported several times in recent years, though the two lesions are not necessarily related.

Polyps which occur during pregnancy often contain decidua and are called decidual polyps, or "deciduoma of the cervix." Decidua appears so frequently at the cervical os, evidently from some endometrial stroma present in the endocervix, that it cannot be considered an unusual lesion. Sometimes the decidual polyp is quite sizeable, and may

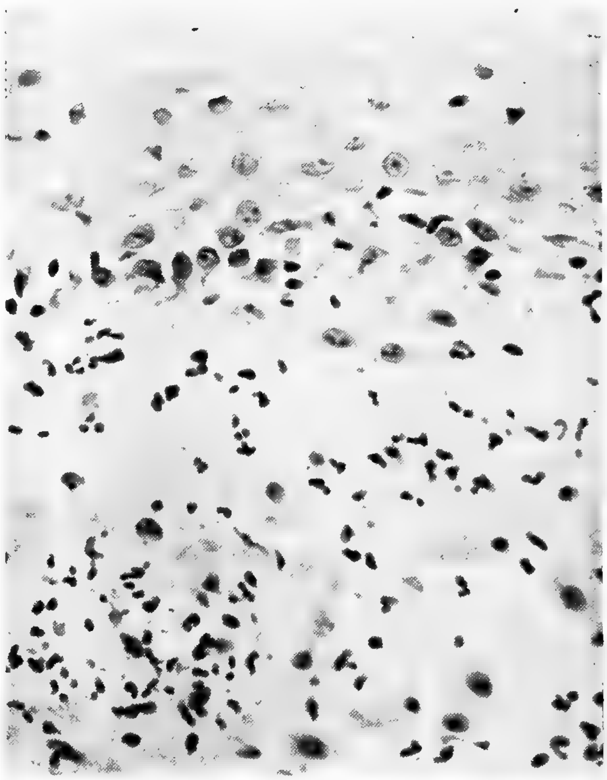


Fig. 67. Deciduoma of the cervix. The very pale-staining squamous epithelial cells at the surface with slightly irregular appearing basal cell layer are not contributory. Within the stroma beneath this epithelium are large pale-pink-staining cells, each having particularly large cytoplasm. These represent decidual cells arising from misplaced endometrial stromal cells down in the cervix. These pink, soft, velvety lesions are frequently seen in pregnancy and are benign.

extend three or four cm. into the vagina. Again these polyps usually are associated with eversive cervicitis, which is more obvious and more severe in pregnancy. Excision of polyps during pregnancy ordinarily is indicated, but must be performed with great care, because of the profuse bleeding that may follow their removal, and because of the possibility of causing an abortion or miscarriage. Preferably, excision in pregnant women should be performed with gentle manipulation in the operating room, under pentothal anesthesia. The base of the excised polyp may be cauterized with silver nitrate, and a packing may be inserted gently against the cervix for one or two days. The deciduoma of the cervix is essentially harmless, but one must never disregard the possibility of malignant tumors which cannot be differentiated on the basis of the gross appearance.

SQUAMOUS METAPLASIA OF CERVIX
EPIDERMIZATION OF CERVIX

Squamous metaplasia of the cervix is a frequent histologic finding, and has no characteristic clinical appearance. This is a condition in which squamous cells are present beneath the single layer of columnar epithelium of the endocervix. Particularly, the cells occur around the endocervical glands, often squeezing the gland down to a minute lumen, at times so that no lumen can be seen. There may be present only masses of squamous cells, as islands, and a perusal of many such islands may be necessary to find a gland of compressed endocervical cells, which provides the clue to the true nature of the lesion. The metaplasia may represent a metaplastic change from the columnar cells into the squamous-like cells, which seems unlikely; the squamous cells from the portio vaginalis or external part of the cervix may grow up underneath the columnar cells and this seems quite possible; or, as a third possibility, the squamous cells may rise from the "reserve cells," which are considered to be embryologic squamous cells left in the endocervix at the time of the recession of the squamous epithelium from high in the cervix during fetal life. A number of investigators believe that the latter explanation is correct. This may well be true, since areas of squamous metaplasia may be found high above the junction of squamous and columnar epithelium.

Squamous metaplasia is seen frequently in everted cervicitis, where portions of the raw, brilliant-red eversion appear slightly glazed over. In these areas, squamous epithelium may have grown up over ulcerations to quickly cover them, or squamous epithelium may seem to have grown beneath the columnar epithelial cells, as a reaction to various

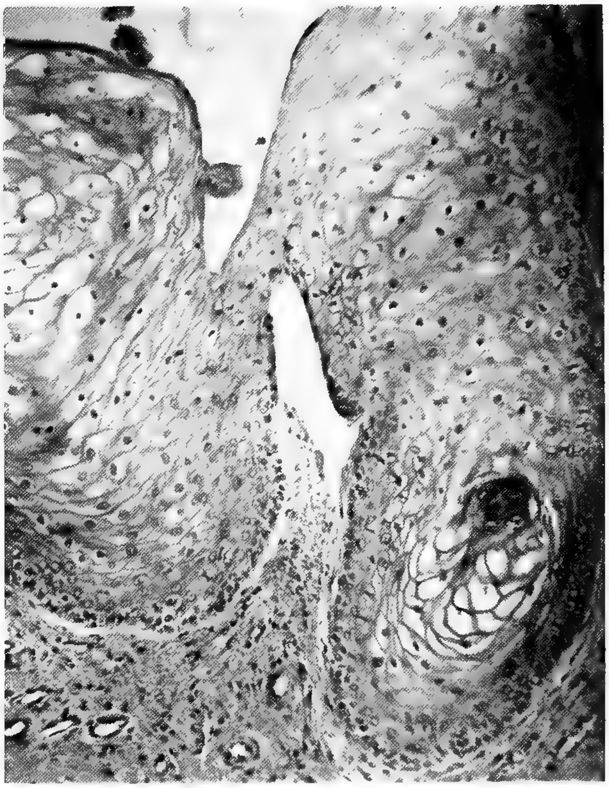


Fig. 68. Epidermization of the cervix. A marked proliferation of the squamous epithelial cells, maturing readily, extending rather deeply into the cervix, perhaps filling scars or defects, is obviously benign. The slight pearl formation is due simply to the intense cornification.

factors. Squamous metaplasia is seen so frequently in cervical polyps as to be almost characteristic. Squamous metaplasia is often found high in the cervical canal. At any rate, it is known that squamous metaplasia may be produced by hyperestrinism alone, by chronic irritation alone, or by a combination, which produces more extensive metaplasia. Barnes, and others before him, have shown that the monkey's cervix will develop increasing degrees of metaplasia if estrogen is injected at frequent intervals, that a similar metaplasia may follow if the cervix of the monkey is scratched daily with an orange stick, and that the metaplasia is much more marked if the two factors are combined. It seems likely that squamous metaplasia in the human cervix is related to excessive estrogenic hormone from the patient's ovaries or placenta, and to chronic irritation due to low grade inflammation.

Epidermization of the cervix is closely related to squamous metaplasia. At times, epidermization represents metaplasia, in which the glands are not seen in the center of the islands of squamous cells. On the other hand, a projection down into the stroma of squamous cells with intact basal layer is frequently seen in the cervix. This may cause concern regarding the possibility of invasive carcinoma, but when the regularity of the cells is observed with their pale appearance, intact basal layer and normal polarity, the benign character is reasonably obvious.

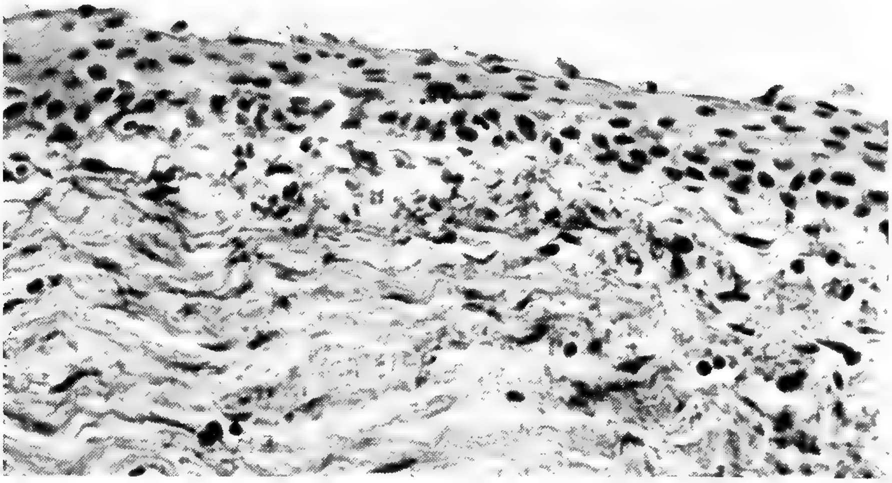


Fig. 69. Senile cervix. Note the thin squamous epithelium four or five layers thick. The basal cells are somewhat irregular but are normal.

Occasionally squamous metaplasia, or epidermization of the cervix, may be difficult to differentiate from carcinoma of the cervix, but, as a rule, the differentiation can be made readily. These two reactions are considered entirely benign and not antecedent to invasive carcinoma.

BASAL CELL HYPERPLASIA, BOWEN'S DISEASE, AND DYSPLASIA OF CERVIX

When multiple biopsies of the cervix or multiple blocks are taken from a cervix for microscopic study, hyperplasia of the basal cell layer up into the spinal cell layer is seen quite often. This proliferation of five or ten layers of the basal cells, with increased frequency of mitoses, is indicative of accelerated growth. This change, associated with some of the cells, has been suggested for a long time as possibly the earliest pre-pre-cancerous change in the cervix. Galvin, TeLinde, and others, have felt that this relation is even more definite, though very many years may intervene before cancerous changes develop. On the other hand, evidence in favor of the relation of these relatively slight changes to malignancy seems very flimsy because of the extreme frequency of basal cell hyperplasia, apparently related to degrees of chronic inflammation, and because apparently a great length of time elapses before this change has been connected with carcinoma of the cervix. For practical purposes, a cervix is never treated as a precancerous cervix on the basis of basal cell hyperplasia alone.

Bowen, in 1912, reported two cases with reddish granular skin lesions, with proliferation of the basal cells up into the spinal cell layer, with marked irregularity of size and shape of nuclei, intracellular edema, intranuclear edema, occasional giant nuclei, and increased mitoses, some of which appeared to be abnormal. But there was a fair degree of maturity of the cells as they approached the surface of the squamous epithelium. This disease later received the eponym "Bowen's

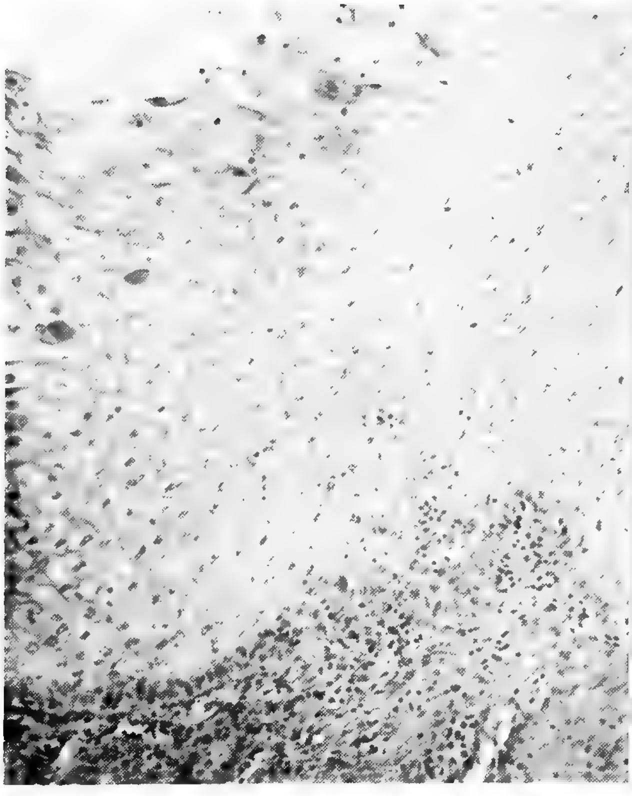


Fig. 70. Edema of the squamous epithelial cells with moderate chronic inflammation. The epithelium here is thicker than normal. The cause of this swelling of the cells may be related to inflammation or to hyperestrogenism. Probably it is not significant.

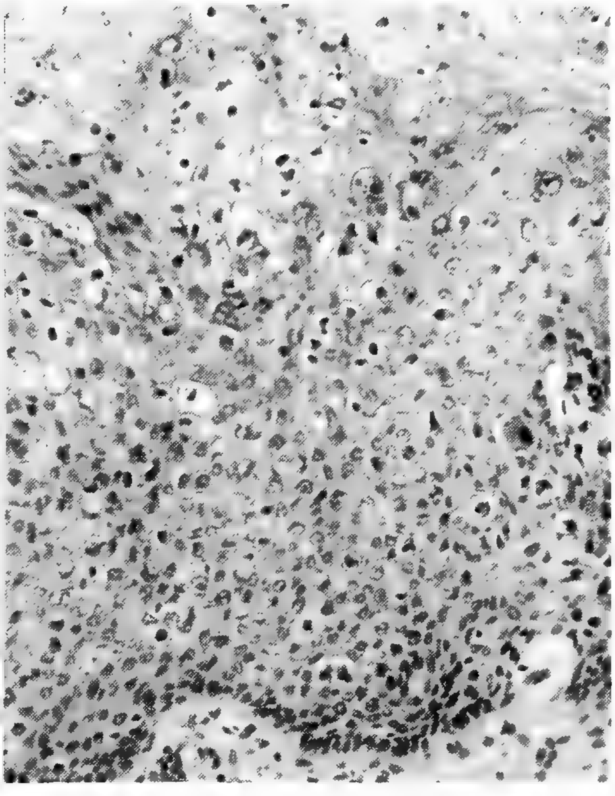


Fig. 71. Bowen's disease of the cervix, or dysplasia of the cervix. This is the typical appearance of a change in the epithelium described by the dermatologist many years ago. The basal cells are extending into the spinal cell layer, but there are degrees of maturation at the surface. The variation in the size and shape of the cells, particularly the intra-cellular edema, hyalinization of cells, and changes in the nuclei are characteristic of this lesion. In the cervix this finding is considered distantly related to invasive carcinoma, and probably it is pre-malignant. This may be associated with obvious carcinoma-in-situ in adjacent areas.

disease." It is widely accepted that this lesion tends to develop into squamous cell carcinoma over a period of years, sometimes ten or fifteen years from its onset. The disease has been described in various parts of the body, particularly on the surface epithelium of the vulva, in the mouth, the esophagus, the trachea, and even the cornea of the eye. Some twenty or twenty-five years ago, this term was used frequently in describing similar lesions of the cervix, which were felt to be precancerous over a long period of time. As increasing understanding of the precancerous lesions of the cervix were established, it became clear that the lesion, carcinoma-in-situ, must show much more anaplastic changes than that which occurs in Bowen's disease, particularly the added feature of extension of the basal cells throughout the spinal cell layer to the surface of the squamous epithelium. Lesions previously considered Bowen's disease of the cervix now are incorporated in the term "dysplasia" of the cervix. Dysplasia includes a variety of changes which are somewhat more florid than basal cell hyperplasia and somewhat less atypical than carcinoma-in-situ. Undoubtedly, many of the excellent examples of dysplasias of the cervix should be considered analogous to the dermatologic lesions known as Bowen's disease, but since the latent period from onset to development of invasive carcinoma seems to be so long, there is less need of radical or destructive therapy for the eradication of these lesions when they occur in the cervix. At present, they are usually treated by cauterization or conization of the cervix, the latter being preferred as a sharp-knife (so-called "cold" knife) conization, allowing the cervix to heal in cleanly. This is followed by Papanicolaou cytology studies every three to six months. This extraordinary group of cel-

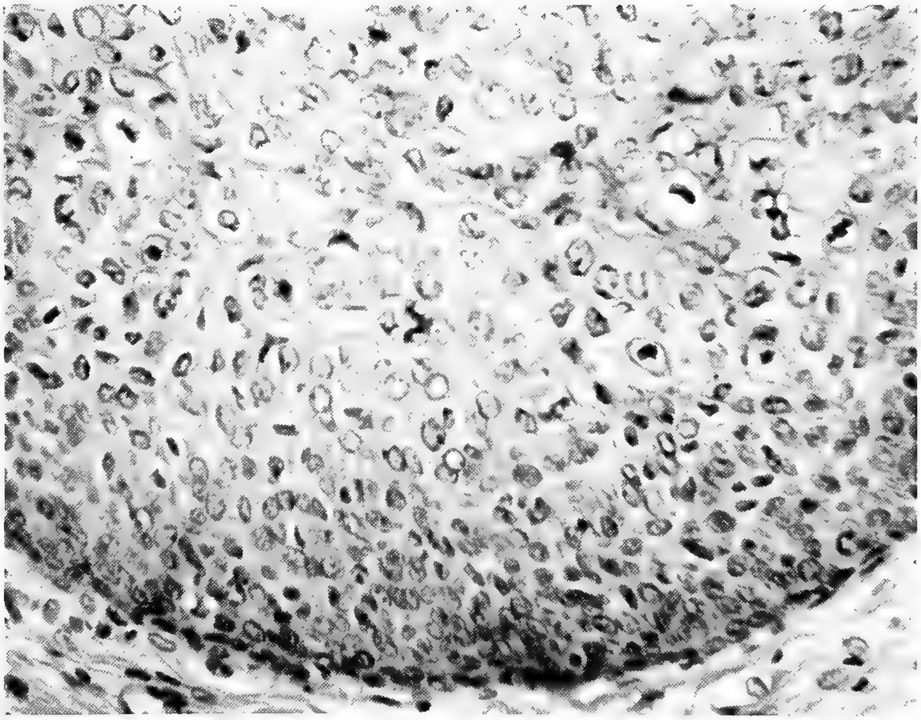


Fig. 72. Dysplasia of the cervix. The epithelium here is much thicker than normal, and shows proliferation of the basal epithelium, but with some degree of maturation more superficially. Many of the cells are quite large, have marked intra-cellular edema and marked irregularity of the nuclei. Mitoses are relatively frequent. While this particular lesion might not be classified as carcinoma-in-situ, in other sections from this case there were found areas of severe and typical carcinoma-in-situ.

lular changes in the squamous epithelium of the cervix will be studied intensively in research centers for some years, before one will know how to classify them more exactly and be able to predict their probable course and significance.

CARCINOMA-IN-SITU OF THE CERVIX UTERI

A more fascinating, and more thoroughly discussed and written about lesion, a more important lesion, than carcinoma-in-situ of the cervix, cannot be imagined in gynecological disease, or in human pathology for that matter. The term "carcinoma-in-situ" was first coined by Broders of The Mayo Clinic, who described the changes in epithelium of various organs that appeared to be malignant, but remained on the surface, without apparent invasion. In 1912, Rubin reported one case in the cervix which fits this description. Earlier than this, Schottländer and Kermauner in 1912 described surface carcinoma around the edges of invasive, ulcerating carcinoma of the cervix. This they called "Randbelag," and it is well known to occur commonly at the present time. "Randbelag," or surface change around truly invasive cancer, may be interpreted only as carcinoma-in-situ, if the invasive areas are not seen. Associated invasive cancer must be ruled out before the diagnosis of carcinoma-in-situ in any case is justified. Schiller in Germany, in 1927, began to record his observations on changes in the cervix uteri which he considered were surface cancer, without any evidence of invasive cancer, but which he thought was a premalignant lesion. In 1934, Schiller visited this country and introduced his ideas here. Emil Novak

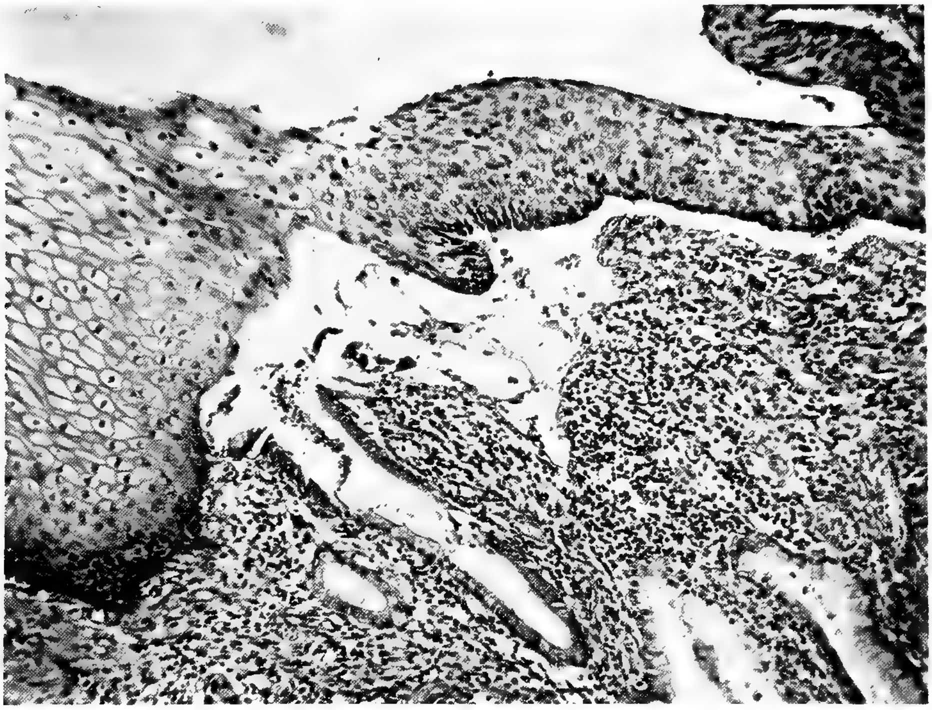


Fig. 73. Dysplasia of the cervix. The squamous epithelium on the left is thicker than normal with edema of the squamous cells, but is benign. That on the right shows changes in the squamous epithelium with lessened maturity and some irregularity of the cells. A marked inflammation beneath the squamous epithelium and about the endocervical glands may be a factor in the changes in the squamous epithelium. It may be most difficult to determine whether this lesion has become sufficiently extensive to be called carcinoma-in-situ.

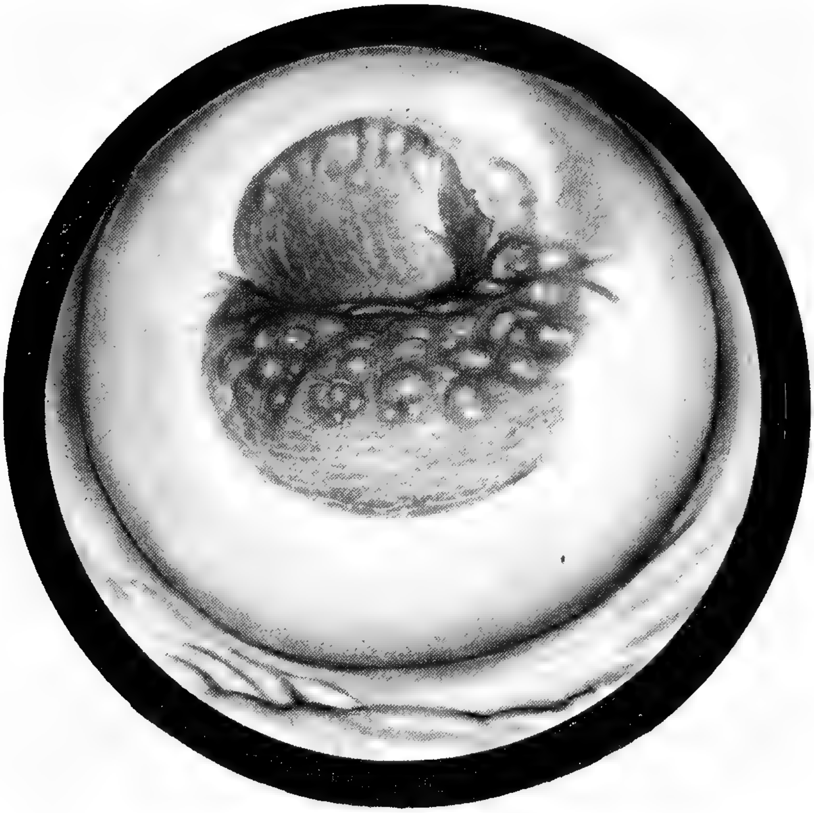


Fig. 74. Carcinoma-in-situ was present in this case with chronic eversive cervicitis. Note the slight bilateral lacerations, the many small cysts of the endocervical glands and the white and grayish streaks, which represent the attempts of squamous epithelium to heal the inflamed eversion. A single biopsy had been taken at 2 o'clock. The diagnosis was made by cytology, biopsy and conization studies.

was much impressed and stimulated the Hopkins Gynecological Laboratory to study this problem in detail. Shortly, a paper appeared by Stevenson and Scipiades (1938), the first in the English literature, describing carcinoma-in-situ in eighteen cases. Invasive carcinoma followed in two cases three and eight years later. At that time, there was a tendency to call these lesions Bowen's disease, after the dermatologist who had described the lesions of the skin, as detailed in the preceding pages. It was soon realized that Bowen's disease shows maturation of cells at the surface of the epithelium, whereas true carcinoma-in-situ lacks this maturation and the abnormal basal cells extend completely through the squamous epithelium. This was emphasized especially by Hertig in recent years.

At present, these variations of lesser degree than carcinoma-in-situ are generally called "dysplasias" of the cervix. In some cases, the basal cells may extend completely through the spinal cell layer, but retain their regularity and have few and normal mitoses. Only lesions with quite abnormal appearing cells are called carcinoma-in-situ; at least, this seems to be the tendency today. For some twenty years, it has been realized that carcinoma-in-situ tends to grow down into the endocervical glands. This is called "gland invasion," and originally was thought to represent a form of invasive carcinoma (TeLinde). Now it is no longer considered to represent invasive tumor at this stage, but simply an extension into the opening of the glands from the surface, with displacement of the columnar epithelium. It may be exceedingly difficult to determine that these collections of abnormal cells are in a gland, particularly if all of the columnar epithelium has been destroyed. Most of the time a small amount of columnar epithelium remains, giving the tell-tale sign of "gland invasion," and not invasion of the "stroma," or the cervix itself. The histologic criteria for the diagnosis of carcinoma-in-situ vary widely, but the tendency is to restrict the term more and more to certain rigid requirements: extension of the basal cells completely through the spinal cell layer, absence of maturation, presence of cytologic pleomorphism, and the presence of abnormal mitoses. Even with such rigid criteria, one must be exceedingly careful to exclude the phenomenon of "Randbelag." It is extremely difficult at times to determine whether or not there is invasion of the stroma.

An increasing number of papers have appeared in recent years to indicate the carcinoma-in-situ may develop into truly invasive, destructive and lethal carcinoma of the cervix. This is indicated in reports describing patients who have been under observation and have developed clinical lesions. More encompassing papers have reported series of patients with obvious clinical carcinoma who have had biopsies taken many years previously. A review of the old sections has revealed foci of carcinoma-in-situ in many. These retrospective studies indicate a relationship.

On the other hand there are other characteristics of this disease that are difficult to

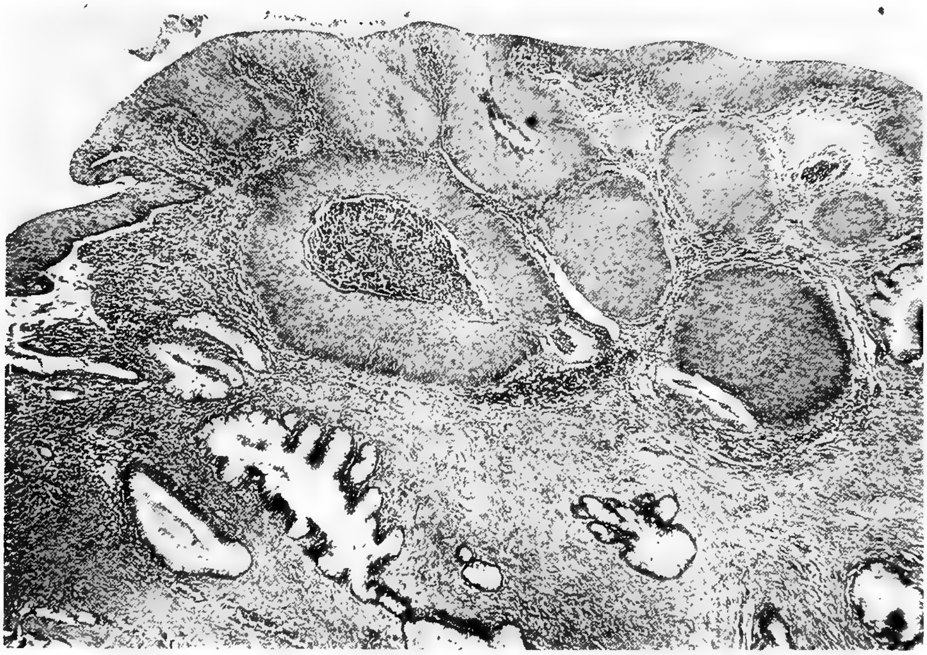


Fig. 75. Carcinoma-in-situ of the cervix with invasion of cervical glands. This is in contrast to stromal invasion, the latter meaning the extension of malignant cells into the connective tissue beneath the squamous epithelium. Here a benign condition is represented by the growing down of the squamous epithelium into the crevices of the glands, often displacing the epithelium. As a rule, one may find portions of columnar epithelium. While the squamous epithelial cells here show degrees of irregularity, this presumably is a benign lesion at the present time, though with malignant potentialities. (From case in Fig. 74.)

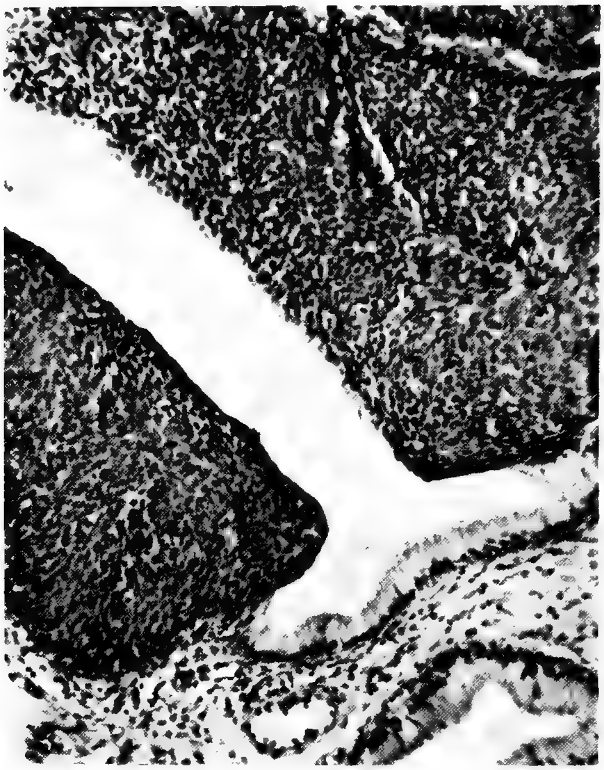


Fig. 76. Another case of carcinoma-in-situ with gland invasion. The extensive growth of the cells and numerous mitoses are evident.

understand. The average age of patients with carcinoma of the cervix is about forty-seven years of age; the average age of patients with carcinoma-in-situ is about thirty-seven years, a ten year difference, which would seem logical because the life history of the disease is commensurate with such a long latent period. If the disease requires ten years to develop, should there be ten times as many in-situ lesions as invasive lesions discovered in a given year, as shown by some investigators? (Some recent reports have a ratio of three to one.) It is evident that, if the lesion lies dormant for a number of years, there should be many more in-situ lesions than invasive ones, but are there too many and do they irrevocably become invasive? The greatest number of in-situ lesions should be found at forty-six years, immediately before the greatest incidence of true carcinoma. It would seem that some of these lesions may regress since the peak incidence of carcinoma-in-situ is thirty-seven years, and diminishes thereafter, whereas the peak incidence of carcinoma of the cervix is forty-seven years.

The incidence of carcinoma-in-situ during pregnancy is rather high, apparently higher than in non-pregnant women. The lesion during pregnancy may appear exceedingly malignant, though with intact basal cell layer, and may give rise to great concern for the safety of the patient. Some of these lesions proceed into truly invasive carcinomas before the end of the pregnancy and during the immediate puerperium. On the other hand, the tendency of the obstetrician and gynecologist is toward conservatism, especially when pregnancy is involved. With the conservative approach, the majority of the patients have not had difficulty during the pregnancy, and it has been apparent in some that the lesion has disappeared in the puerperium. On the other hand, in the majority of instances the lesion tends to remain the same after delivery as

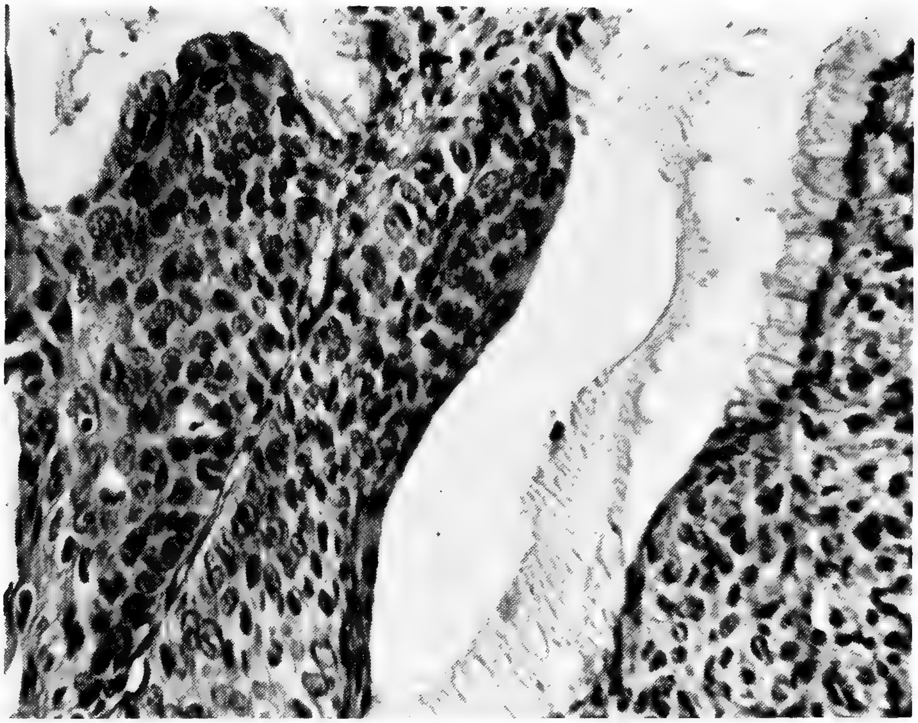


Fig. 77. High power view of carcinoma-in-situ from the previous case in low power. The basal epithelial cells are growing to the top of the epithelial layer. There are loss of polarity and increased mitoses. No evidence of invasion was seen.

before (Greene), and to have the malignant potentialities for the future. This strange lesion is probably no different in the nonpregnant and in the pregnant, although many leading obstetricians believe there is a difference, and that the lesion is much less serious when associated with pregnancy. Certainly, the overwhelming opinion is not to interfere with pregnancy, because the lesion is so slowly changeable, and the risk of invasion before termination of the pregnancy is relatively slight. This problem of in-situ lesions in pregnancy remains a moot one, and is an area for extensive research.

This lesion has been called Stage 0 carcinoma by the League of Nations classifying committee. It has been suggested that it should be removed from the category of true carcinoma and be labelled in a different manner than Stage 0.

The clinical appearance of carcinoma-in-situ of the cervix is not characteristic. In a small percentage, there may be an area of leukoplakia, or white plaque, on the cervix, which may show carcinoma-in-situ on biopsy. On the other hand, this leucoplakia may show only thickening of the epithelium with parakeratosis. At other times, the white spot derives its appearance from an underlying Nabothian follicle cyst, which presses the epithelium upward, the opaque appearance being caused by the mucus in the cyst. Apparently, less than ten per cent of cases of carcinoma-in-situ appear as leukoplakia of the cervix. About fifty per cent are associated with eversion or eversive cervicitis. Within this red, raw appearance (mainly covered by columnar cells or squamous epithelium which has not formed glycogen, and which has not become opaque to the underlying capillaries), minute whitish or greyish areas may represent carcinoma-in-situ. Biopsy of four quadrants will permit discovery of the majority of these lesions. In another forty per cent of the cases, or even more, the lesion seems to be entirely endocervical, growing up among the glands of the endocervix from the reserve cells (small, squamous-like cells that occur in patches underneath the columnar cells of the endocervix). Thus it is obvious that biopsies of the external cervix alone will miss the lesion in the endocervix, which make up such a large proportion of cases. Now that there are available technicians with sufficient training to distinguish these abnormal cells that are shed in the cervical secretions, the disease may be discovered more readily than with random biopsy of the cervix. It is uncanny to see the detection of this lesion so accurately in routine cytology studies. The smears are taken first by a swab of non-absorbent cotton extending high into the endocervical canal, followed by scraping of the cervical os with Ayre's wooden spatula. Some aspirate the cervical canal, and others favor the original method of aspiration of vaginal secretions from the posterior fornix of the vagina.

The treatment of carcinoma-in-situ of the cervix is controversial. The majority of obstetricians and gynecologists in this country believe the best treatment is total hysterectomy, conserving the tubes and ovaries, re-

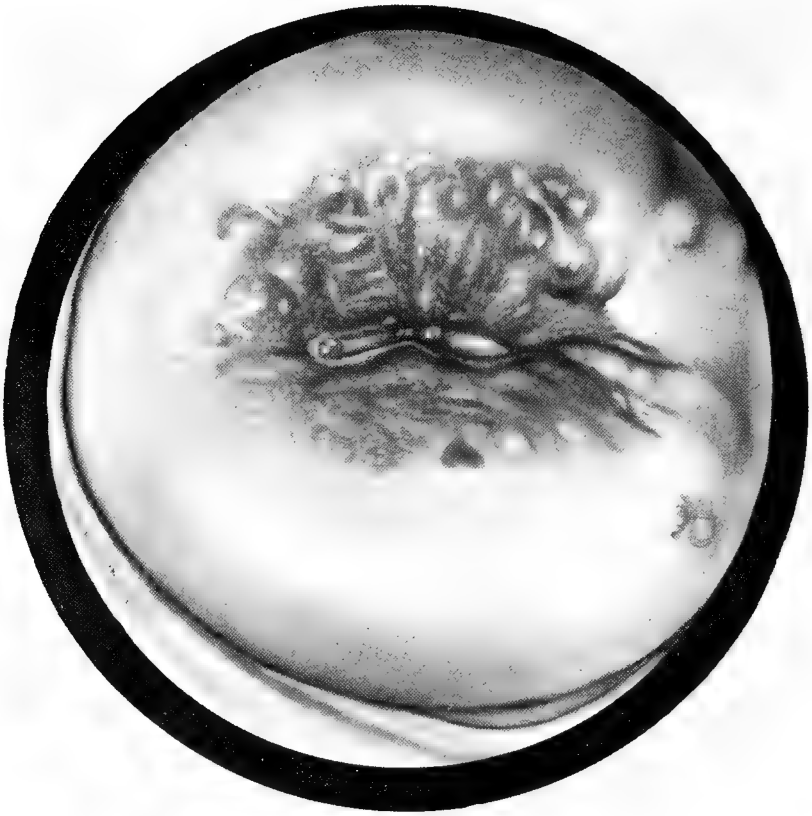


Fig. 78. Carcinoma-in-situ was unsuspected in this otherwise mild chronic eversive cervicitis. The slight lacerations have followed deliveries many years ago. Small cysts are evident, particularly laterally. The irregular grayish borders of squamous epithelium have been attempting to grow over the inflamed everted endocervical epithelium. The diagnosis was made by cytology and conization studies.

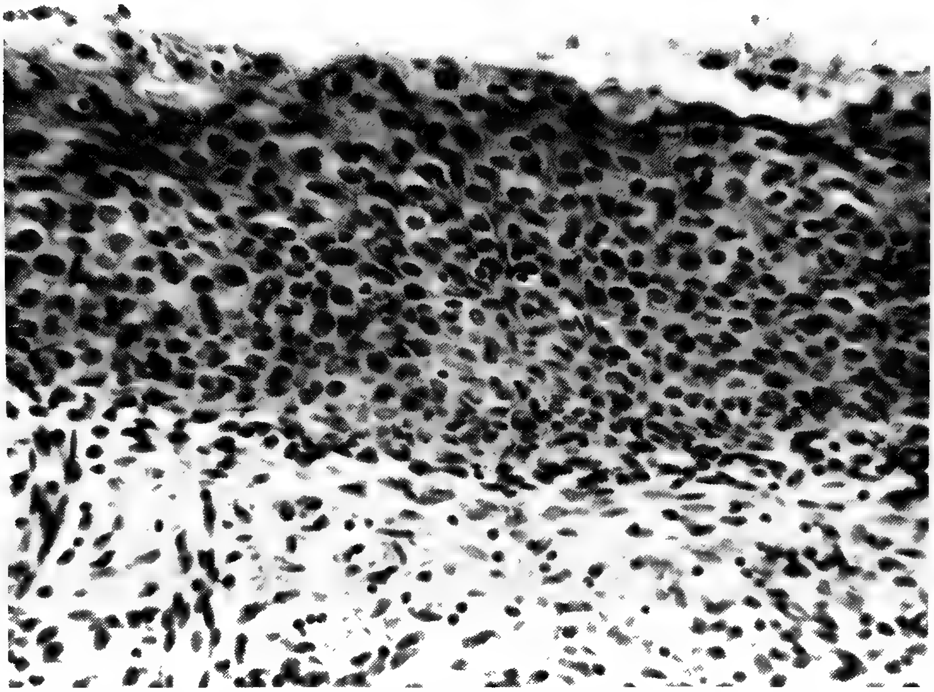


Fig. 79. Carcinoma-in-situ of the cervix. The basal cells have extended entirely through the squamous epithelial cells, have lost their polarity in moderate degree, show considerable irregularity of the size and shape of the cells and there is a slight chronic inflammation beneath the epithelium. No evidence of invasion was seen. (From case in Fig. 78.)

moving the cervix with a small cuff of vagina about the cervix. This view has been advocated in numerous publications by TeLinde, and others. Perhaps many uteri have been sacrificed because of this diagnosis, even when made very accurately, because there does remain doubt that all of these lesions inevitably become invasive carcinomas. Which is the real and dangerous premalignant lesion remains the question today. Is it better to sacrifice two, or five, or ten uteri to save one woman from a death of cancer, particularly if these women have completed their families? Undoubtedly, the latter figure of ten to one is hardly acceptable. The problem of the diagnosis and treatment of young women who have not had children is difficult and serious. Many believe that once the diagnosis is established, treatment should be the same, regardless of age. Others incline to the opinion that cancer is cancer, and precancer is precancer, and each should be treated on its merits. But emotional and sentimental elements enter this problem to an extreme degree. The scientific problem of curing a lesion wihout hysterectomy is important and an aim for the future. Many are recommending that a sharp conization of the cervix be performed without hysterectomy, hoping that the premalignant (never the invasive) lesion may be excised in this manner. This operation is performed essentially for diagnosis, and in the young for treatment.

Sharp conization of the cervix is performed in the following manner. Under pentothal anesthesia in the hospital, after proper cleansing and preparation of the vulva and vagina, the anterior wall of the cervix is grasped with the tenaculum in a transverse position. The canal is sounded to determine its direction. Then with a scalpel with small, sharp blade, a circular area about the cervical os, encompassing all the everted area, if present, is incised, and the tissue is cut in a conical

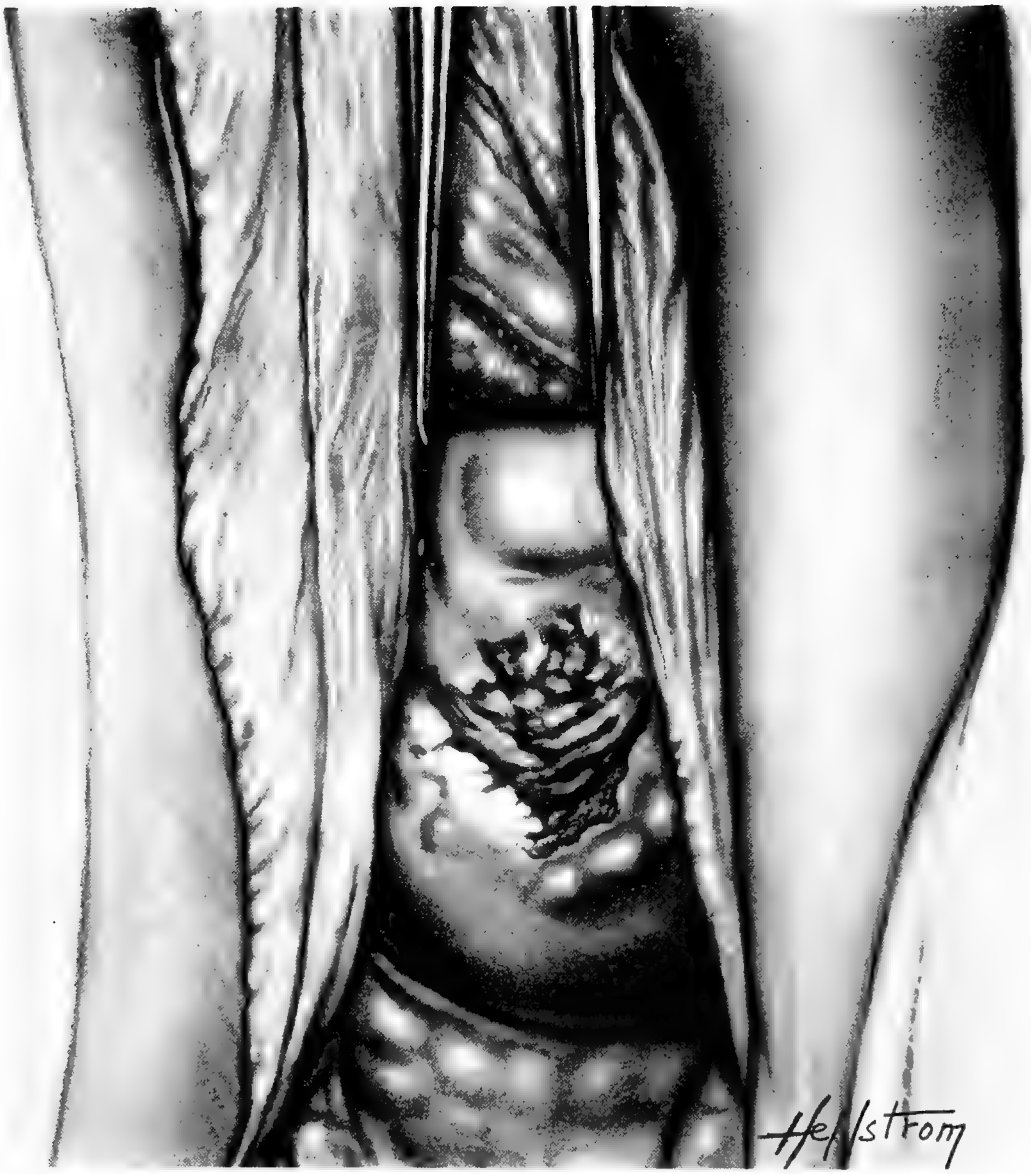
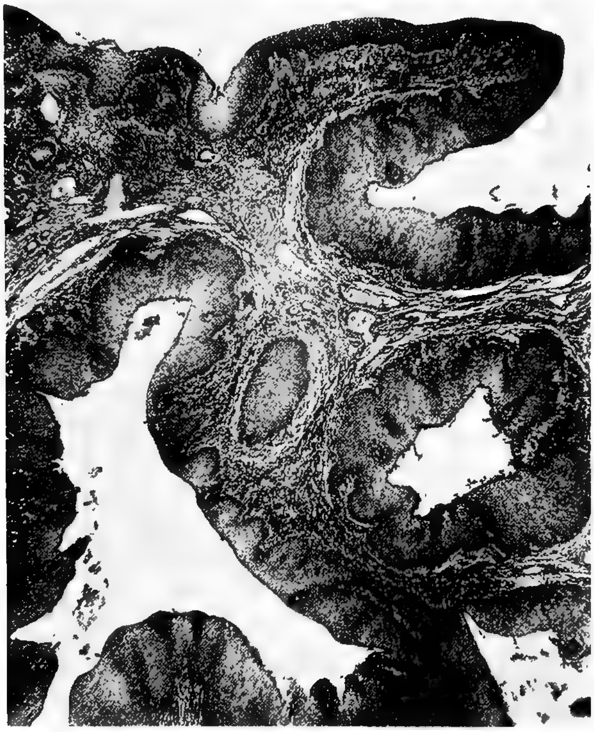


Fig. 80. Leucoplakia of the cervix at 7 o'clock, which represented carcinoma-in-situ in this case. Also present is chronic eversive cervicitis, chronic cystic cervicitis and second degree descensus of the uterus.

Fig. 81. Extensive carcinoma-in-situ of the cervix with marked growth into the crevices of the cervix and into the glands. The dark appearance of the basal type of epithelial cells makes this an outstanding example.



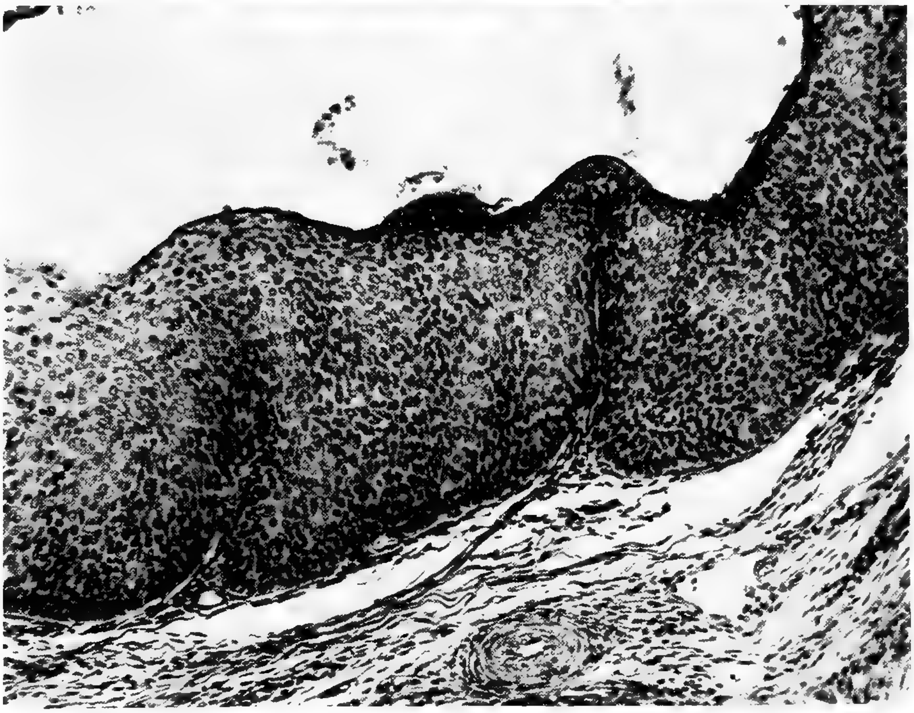


Fig. 82. Carcinoma-in-situ of the cervix, higher power view. An extensive lesion which is invading the glands. As yet it is thought to be benign. (High power from Fig. 81.)

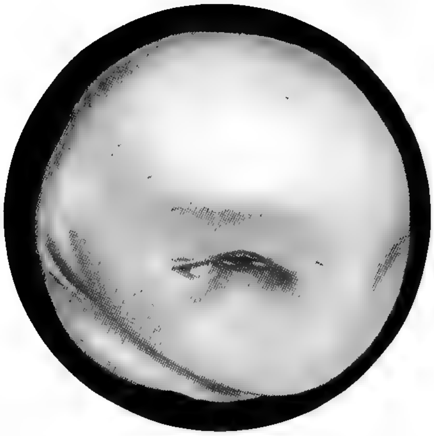


Fig. 83. Carcinoma-in-situ in a normal appearing cervix. The Papanicolaou smear was positive. One biopsy has been taken at 7 o'clock. Conization was performed and multiple blocks were sectioned.

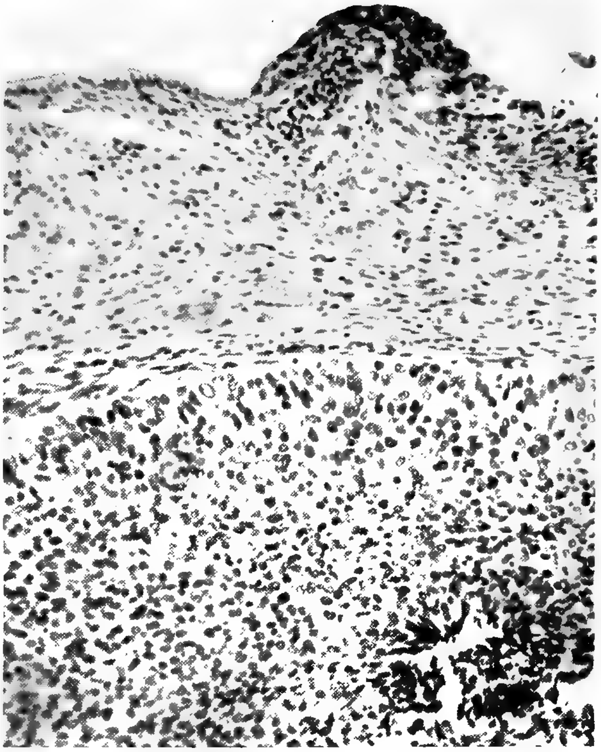


Fig. 84. Early invasive carcinoma of the cervix found incidentally in excised uterus. Difficult to distinguish from carcinoma-in-situ. Two years later patient developed recurrent carcinoma in apex of vagina.

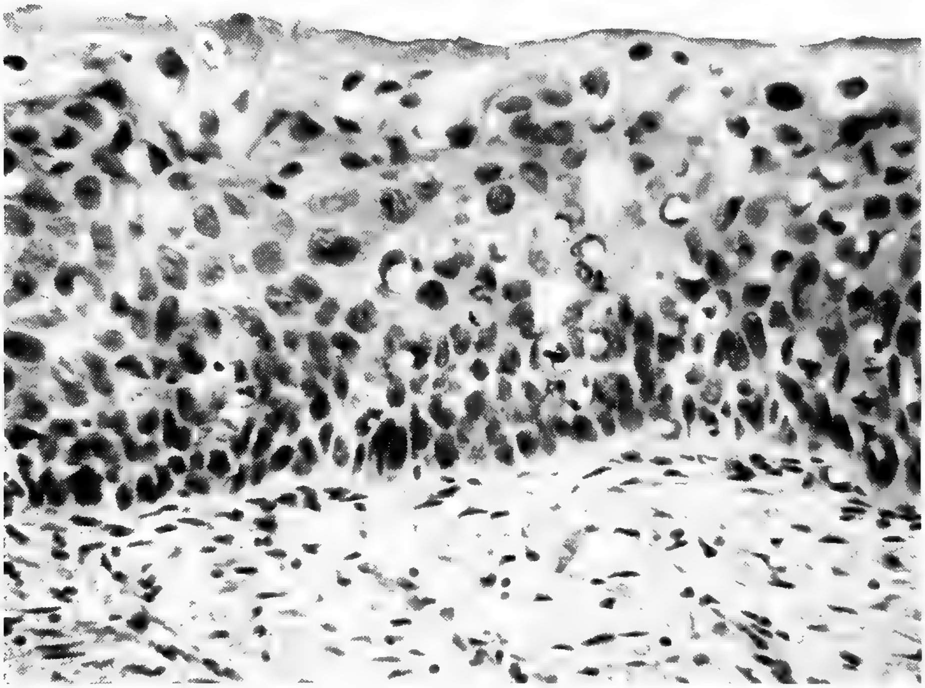


Fig. 85. Carcinoma-in-situ of the cervix. The basal cells are growing up into the spinal cell layer, though there is some cornification and maturity at the surface. There is complete loss of polarity, in which many of the cells are pointing perpendicularly to the surface instead of transversely. There are marked variations in the nuclei, with abnormal mitoses, which tends to the diagnosis of carcinoma-in-situ rather than dysplasia of the cervix.

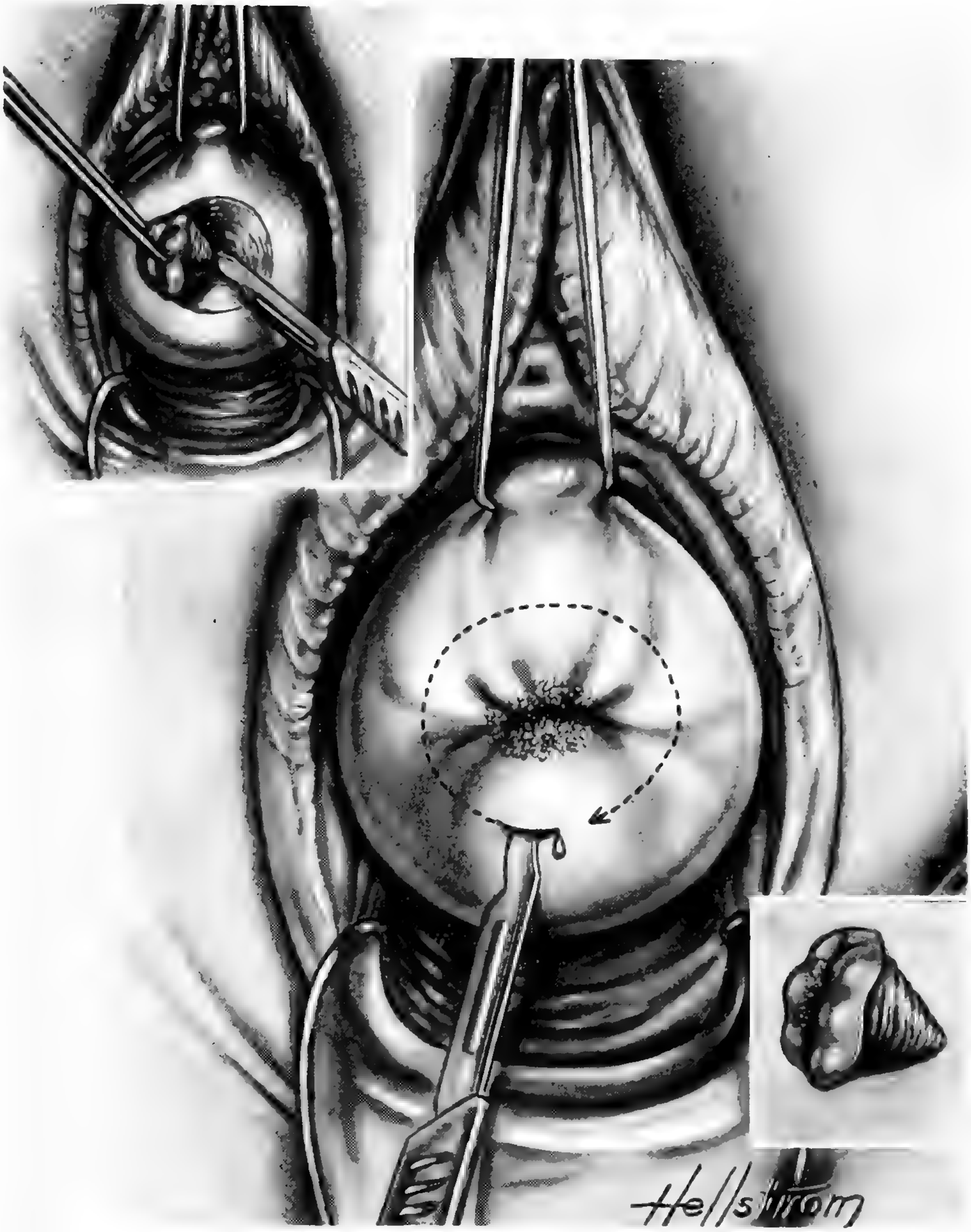


Fig. 86. Conization of the cervix, the so-called "cold-knife conization" or "sharp conization." After sounding the canal, to determine its direction, the cone of tissue is excised by using the scalpel with small blade. Ordinarily if the canal is closed, the specimen measures about 2 cm. in diameter and 2.5 cm. long. A dry gauze packing is changed and reinserted after 48 hours, to be removed at home after a second forty-eight hours.

manner up toward the canal, some two and one-half cm. deep. This incision allows careful microscopic study from sections of multiple blocks taken from around the circumference. Some advocate treatment of all in-situ lesions by this limited procedure, and that the patients be followed by Papanicolaou cytology studies every three to six months. Perhaps

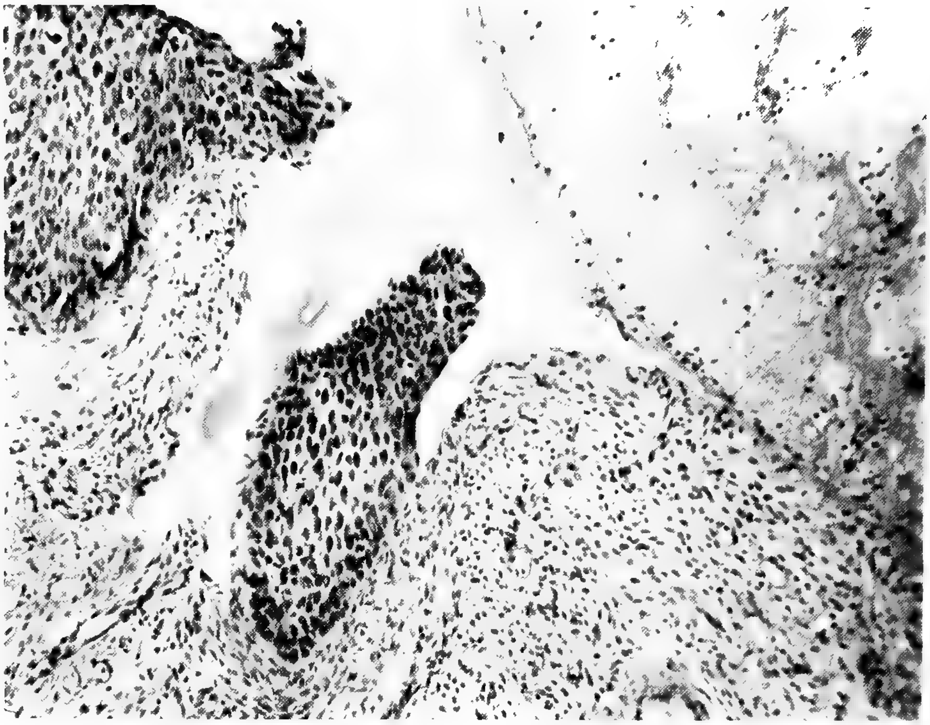


Fig. 87. Residual carcinoma-in-situ of the cervix following a sharp conization. The exudate from the edge of the incision of the cone is shown on the right. The excised uterus of this 47 year old woman shows fragments of a residual lesion, evidently precancerous, with markedly abnormal cells. This illustrates one of the difficulties of treating these patients with the conservative conization. Very careful follow-up by means of Papanicolaou cytology studies is necessary if a conservative approach is used.

this is logical. On the other hand, carcinoma-in-situ has been found in excised uteri higher in the canal in forty per cent or more of cases. This makes one think that conization alone is by no means safe, certainly not in the older patient. With the conservative approach, one depends on the patient persistently having follow-up examinations, and the shedding of cells externally before any invasion of stroma may occur.

A few have applied radium and intensive x-ray therapy to in-situ lesions, as though they were treating invasive carcinomas of the cervix. If there is no definite invasion, such intensive therapy is not advisable, because of the destructive effects of the irradiation on the uterus, bladder, ureters, intestines, nerve tissue and bony pelvis and femurs, as well as causing castration. In unusual instances, smaller dosages of radium may be applied when the patient is not an operative risk, but most would be more inclined to rely on conization alone, if hysterectomy is not performed.

The chapter on carcinoma-in-situ is not closed. Opinion regarding definitive treatment will be crystallized as additional data accumulate. This may come soon or may take years.

CARCINOMA OF THE CERVIX UTERI

Carcinoma of the cervix is one of the most frequently occurring malignant tumors in the female, exceeded in number only by carcinoma of the breast. The incidence would seem to be about three per cent of all women who live beyond the age of forty years. In Kentucky, each year there are about eight thousand deaths in women above the age of

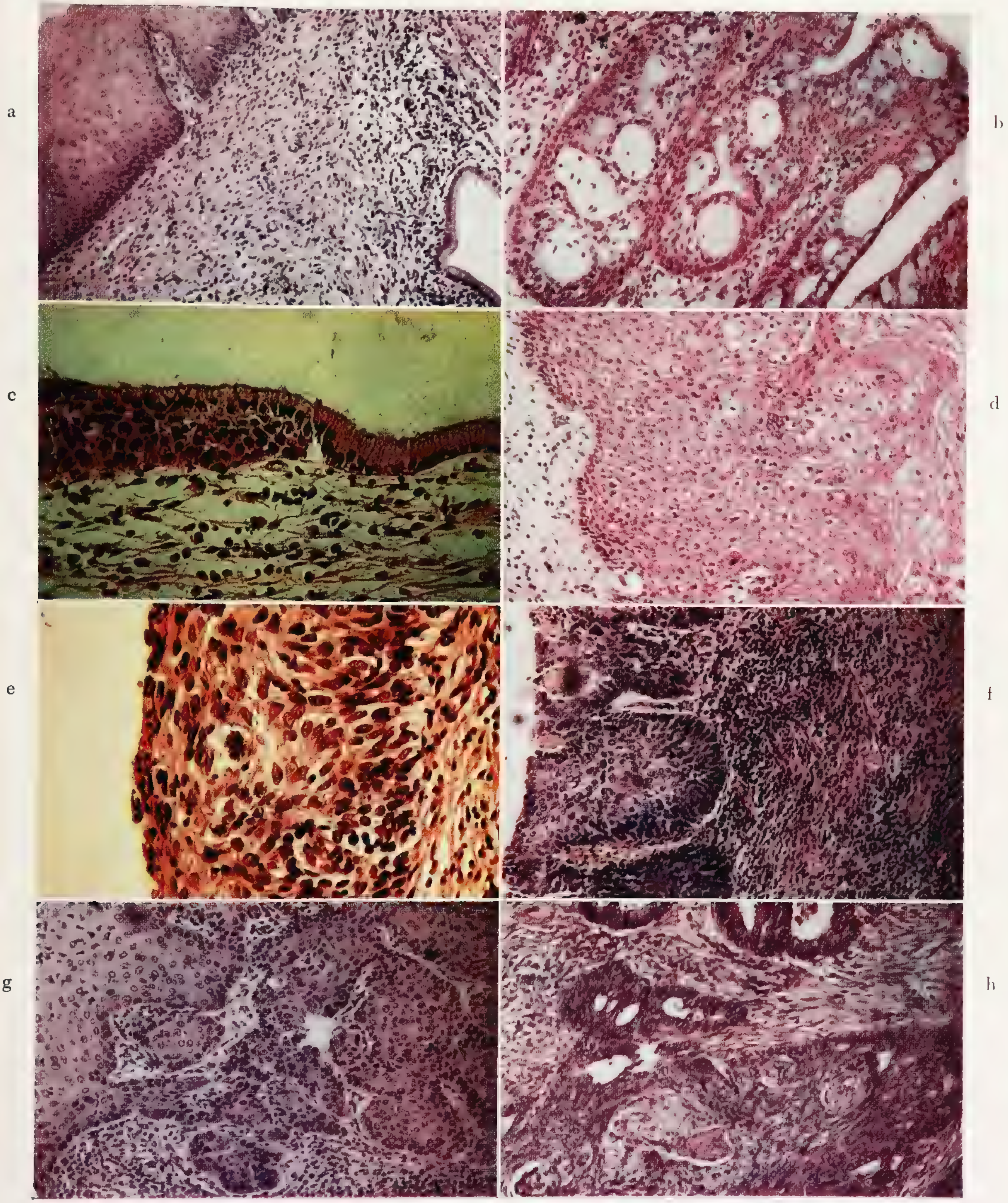


PLATE II

a. Chronic Cervicitis. The squamous epithelium from the portio vaginalis shows a well-defined layer or layers of basal cells, above which the squamous cells show normal maturity. The endocervical gland is lined with the picket-fence epithelium, tall columnar, with basic nuclei. A marked chronic inflammatory reaction particularly surrounds the glands.

b. Squamous metaplasia of cervix. Squamous-like cells surround the columnar cells of the endo-cervix. The latter have become greatly flattened. Sometimes one must examine several sections to find the columnar cells in the central portion of the lesion. This is benign.

c. Reserve cell hyperplasia. Beneath the columnar epithelium from high in the endocervix is a collection of squamous-like cells akin to the basal cells. From these cells, remaining from fetal life, squamous metaplasia, and possibly carcinoma-in-situ and carcinoma, may arise.

d. Dysplasia of cervix (Bowen's disease). The basal cells grow up into the spinal cell layer, but there is partial maturation in the superficial layers. The nuclei show variation in size and shape, with rather many mitosis. Intracellular oedema, intranuclear oedema, and individual hyalinization of cells further characterize this lesion.

e. Intraepithelial carcinoma of cervix. The basal cells have grown up through the spinal cell layer, show marked variation in size and shape. A most striking change here is the complete loss of polarity, the parallel stratification having disappeared.

f. Surface carcinoma adjacent to invasive, ulcerative carcinoma of the cervix (Randbelag). Extremely abnormal cells with irregular and pyknotic nuclei and abnormal mitoses. Undulating and broad rete pegs. This might be mistaken for carcinoma-in-situ, but the appearance is extraordinary.

g. Invasive squamous cell carcinoma of cervix (early). The buds are surrounded by cuboidal cells with particularly abnormal nuclei. Transitional cell type. No pearl formation.

h. Adeno-canthoma of cervix. A mixture of adenocarcinoma and squamous cell carcinoma. Thought to represent adenocarcinoma with metaplasia to resemble squamous cells.

forty; two hundred and seventy or two hundred and eighty of these die of carcinoma of the cervix; approximately one woman of every thirty who dies after forty years. Actually if one-third of the over-all group who have the disease are cured, the incidence of invasive cervical cancer must be about four or five per cent. At any given time, if one hundred women, age forty or more, are examined completely (with smear and biopsy), one per cent, or one patient, will show invasive carcinoma, and two or three patients will have carcinoma-in-situ of the cervix. It is apparent that as these women live out their lives, carcinoma of the cervix is a cause of death in three per cent. Similarly, carcinoma of the breast kills about four per cent of women, carcinoma of the endometrium about three per cent (the incidence is increasing), and carcinoma of the ovary about one per cent of all women after the age of forty. These figures are difficult to understand, and may be used to explain different viewpoints.

Ninety-five per cent of cervical carcinomas are squamous cell carcinomas, arising from the squamous epithelium or perhaps from the "reserve cells" deposited up in the endocervix during fetal life. Five per cent are

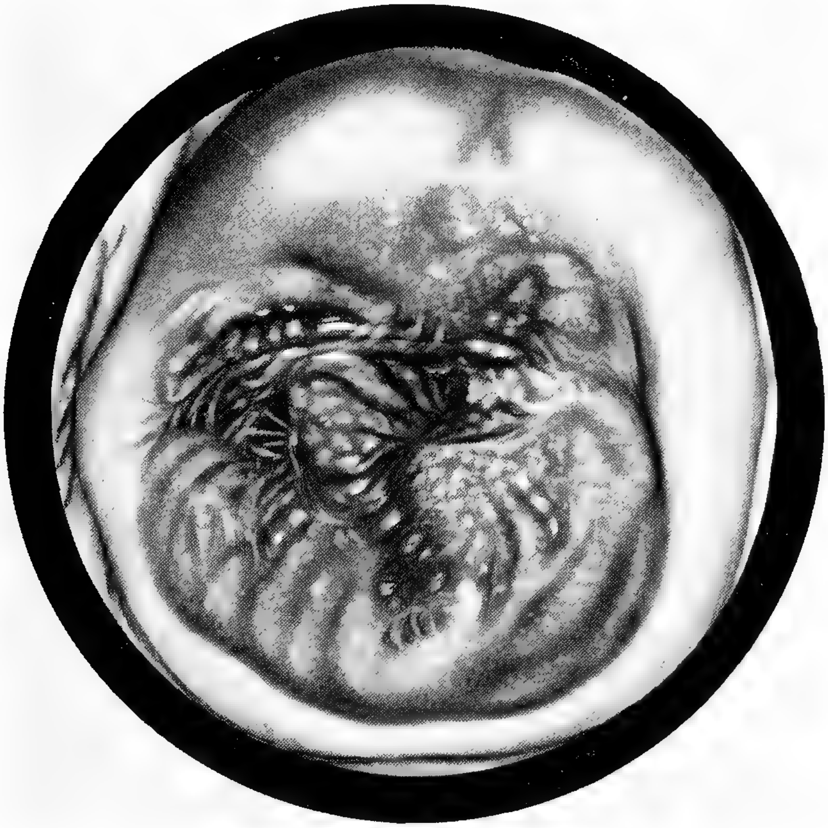


Fig. 88. Squamous cell carcinoma of cervix, clinical stage I. The posterior lip shows a protruding, granular, friable, easily-bleeding growth. The anterior lip shows chronic eversive cervicitis. This was treated with x-ray and radium, with a good result.

adenocarcinomas, arising from the endocervical glands.

Squamous cell carcinoma of the cervix has been divided by Martzloff into three types. This includes the *transitional cell type* of epidermoid carcinoma, which makes up eighty-five per cent of the total, and which has homogeneously staining bluish or pale epithelial cells without cornification or pearl formation. Ten per cent make up the *basal cell type* of epidermoid carcinoma; the cells of this type are quite dark and closely approximated. This type has no relation to basal cell carcinoma of the skin, a relatively benign lesion. It represents the most malignant of all cervical carcinomas. Five per cent of the total are of the *spinal cell type;* the cells show marked cornification and pearl formation. This latter type, being more differentiated, is considered the more slowly growing and the more resistant to irradiation therapy. Other observers do not divide carcinoma of the cervix into these forms, because Martzloff, himself, and many others have shown that any particular tumor may show all three forms in biopsies taken from different portions of the tumor. Still others have used Broders' classification of four grades, the higher grade meaning lesser differentiation, increased malignancy, and greater radiosensitivity. Most believe that this latter classification also is of little value, because of the variation in the

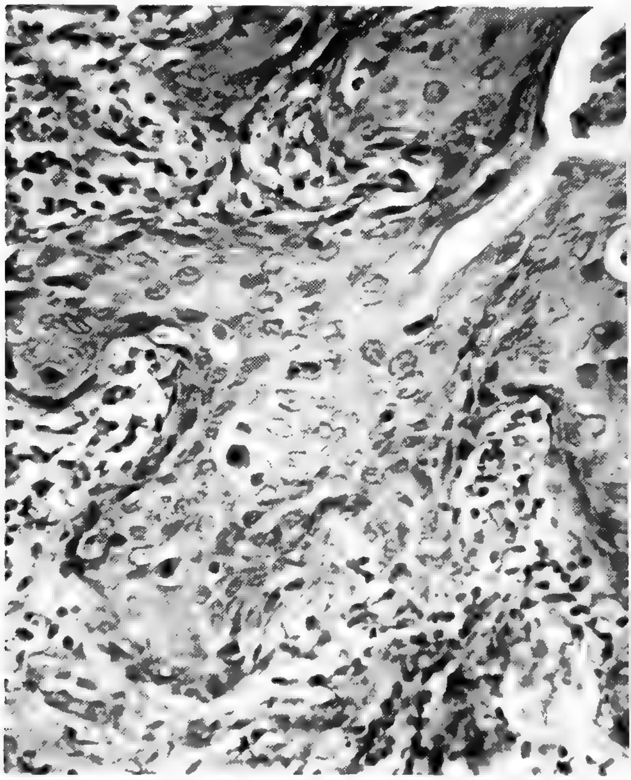


Fig. 89. High power view of invasive squamous cell carcinoma of the cervix. The variation in size and shape of the nuclei and presence of mitoses are readily seen. Inflammation surrounds the invading buds of cancer cells. This shows more cornification than usual.

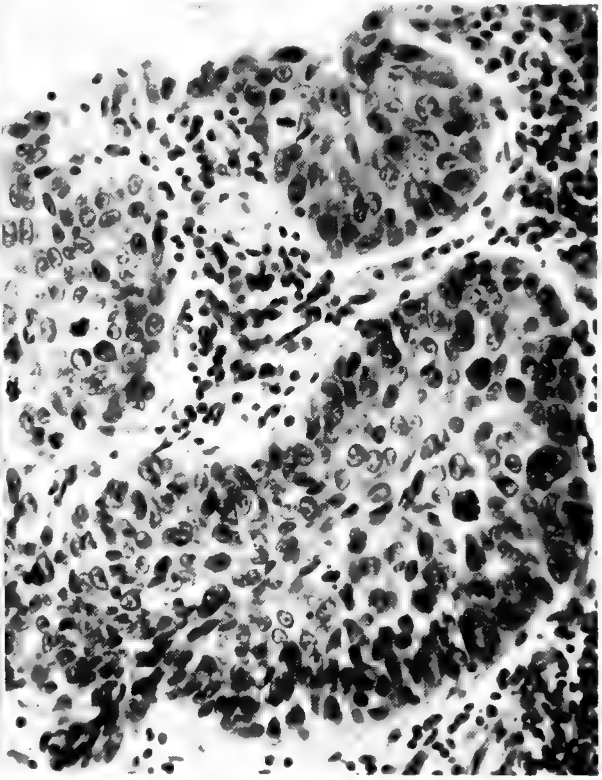


Fig. 90. High power view of an invading squamous cell carcinoma of the cervix showing slight degree of cornification. The edges of the invading tumor seem surrounded by cuboidal epithelial cells. This illustrates some of the difficulties of determining whether or not invasion is present in the very early cancer, especially when areas dipping down into the stroma may seem to be surrounded by an intact basal cell layer. The marked changes in the nuclei here are obvious.

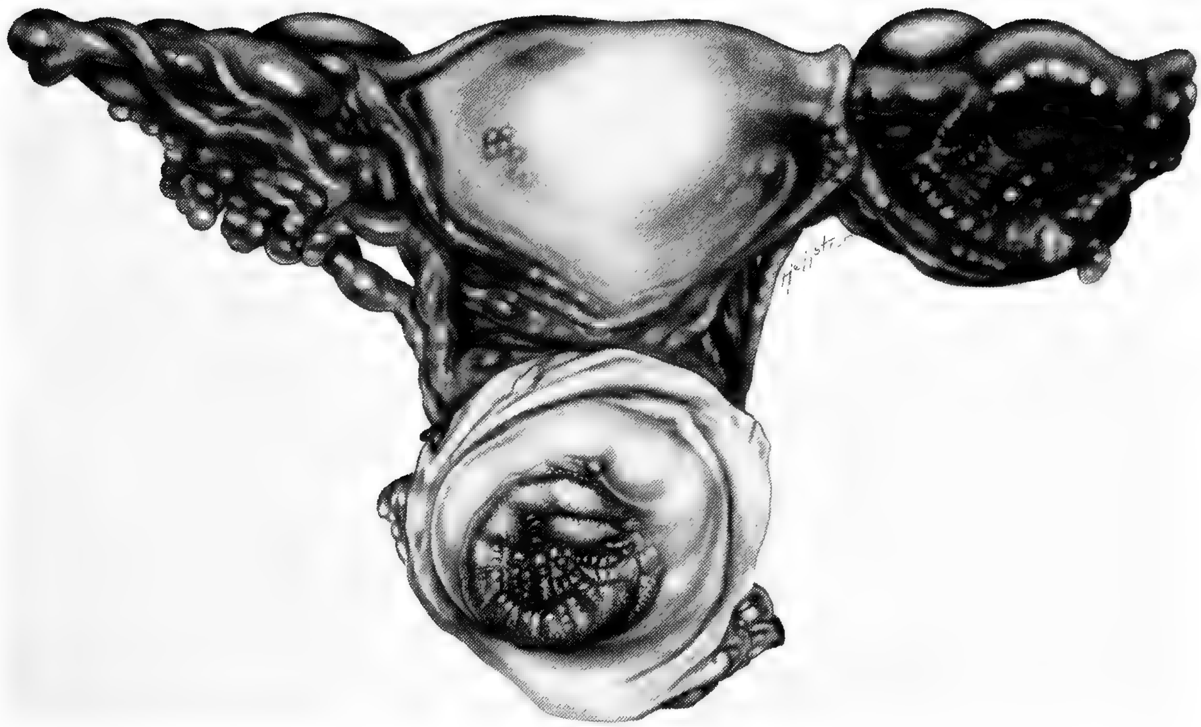


Fig. 91. Squamous cell (epidermoid) carcinoma of the cervix, clinical stage I. The patient, age 26, discovered the growth when inserting her diaphragm. No bleeding. After course of x-ray therapy, there was no change. Radical hysterectomy and pelvic lymph node dissection (nodes not shown) has been followed by cure after 7 years.

individual tumor and the difficulty inherent in determining proportionment of cells numerically.

Adenocarcinoma arises from the endocervix and represents five per cent of cases of cervical cancer. The lesion is somewhat more slowly growing, responds rather more poorly to irradiation therapy. A mixture of adenocarcinoma and squamous carcinoma (adenoacanthoma) is rare, if cases with some degree of squamous metaplasia are not included. Treatment of adenocarcinoma is primarily by irradiation therapy, though some prefer surgery alone, or a combination of irradiation followed by wide surgical excision.

The League of Nations Committee, many years ago, set up a gross classification of four stages, in order that cases might be grouped together to determine the effectiveness of treatment and prognosis. Stage I indicates that the tumor is limited to the cervix. This includes a wide variation from the earliest (microscopic) invasion, to the large exophytic tumors filling and distending the vagina, but without extension onto the vaginal wall, and without induration in the ligaments. Corscaden has suggested that stage Ia should indicate microscopic invasion alone, without any evidence of gross tumor; stage Ib should include gross lesions up to one cm. in diameter; and stage Ic all larger than one cm., but grossly limited to the cervix. This seems a better system of clinical classification. Stage II carcinoma of the cervix indicates not only a tumor in the cervix, but extension onto the vaginal wall in the upper third of the vagina, or into one or both broad ligaments, but not out to the bony pelvic wall. Stage III carcinoma indicates extension onto the vagina below the upper third, or out into one or both broad ligaments to the very wall of the pelvis (a stoney-hard pelvis on one or both sides), or metastasis to a lymph node near the wall of the pelvis (this latter may occur with a very small growth in the cervix, and may be impossible to recognize by pelvic examination). Accurate staging may be very difficult, and findings may be interpreted differently by different examiners. Only exploratory operation can give the true gross staging in many instances. Stage IV carcinoma of the cervix represents those which have extended through the wall of the bladder, through the wall of the rectum, usually with fistula formation, or outside the pelvis by metastases to the lymph nodes above the pelvic brim, or into a distant area, as the colon, liver, lungs, skull and other bones and lymph nodes. This classification is useful, but also has serious defects, which probably cannot be corrected.

The cause of carcinoma of the cervix, as is true of cancer generally, is unknown. For a very long time, childbirth, with its attendant lacerations and cervical infections, was considered a factor. All infections, with eversive cervicitis, or erosions, have been considered important. Good gynecologic treatment includes the eradication of all inflammation possible in the cervix by cauterization, by conization, by repairing lacerations, and by amputations. Cashman reported that several thousand of his patients, who had had cauterization of the cervix, never developed car-

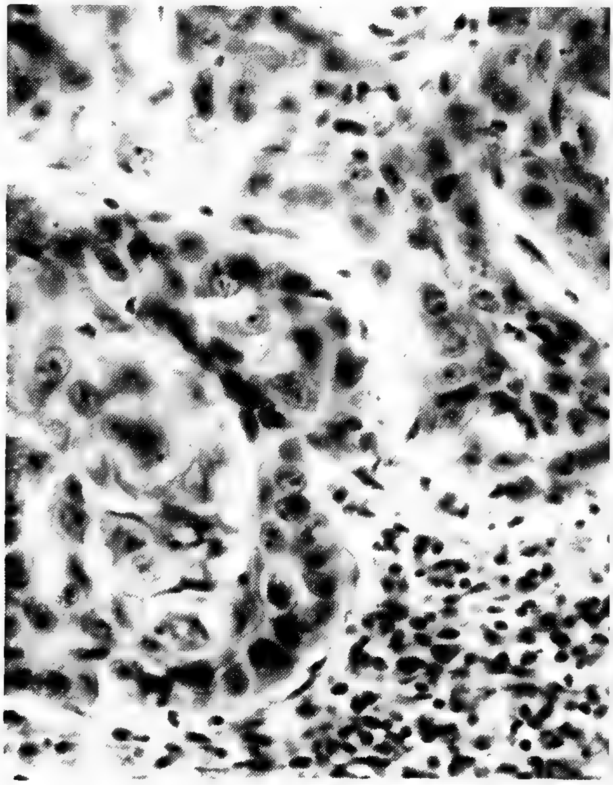


Fig. 92. Invading strands of carcinoma of the cervix. Degrees of cornification of the cells are seen, but also obvious are the variations in the nuclei.

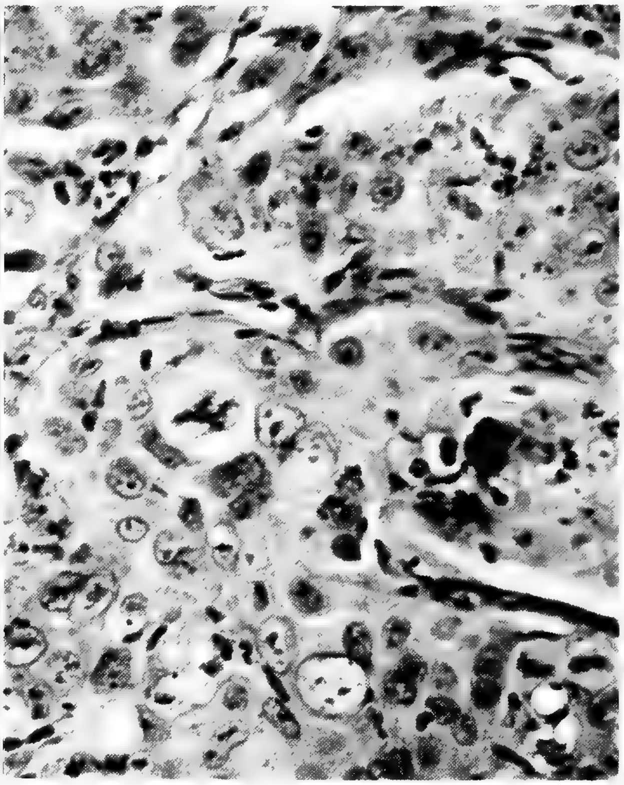


Fig. 93. A high power view of an invading mass of squamous cells showing marked changes in the nuclei, with intranuclear edema, intracellular edema and marked variation in the nuclei with abnormal mitoses.

cinoma of the cervix. This seems to lend credence to the view that infection and chronic irritation may be a factor in the development of carcinoma of the cervix. If not, then the treatment by cauterization must eliminate some other factor that might lead to carcinoma of the cervix.

Other and more recent evidence has given some astounding figures. It seems that the incidence of carcinoma of the cervix is related to the age of marriage, that the younger the patient is married, the more likely the possibility of developing cervical carcinoma in later years. The delivery of children seems not to be a statistical factor. This suggests that sexual relations at an early age may be an important factor. There is the old bug-a-boo of the smegma from the male, which has been shown to be carcinogenic in mice. Smegma always is implicated, when it is noted that carcinoma of the cervix rarely occurs in Jewish women (one-tenth as frequent as in non-Jewish). Circumcision of Jewish men, preventing the accumulation of smegma, has been suggested as the reason for infrequent cancer in Jewish women. However, there may be a racial difference that is far more important than circumcision. The almost routine circumcision of non-Jewish male children in recent years should provide convincing evidence in the future.

Another interesting point is the report by Gagnol of the absence of carcinoma of the cervix in a large number of Catholic nuns.

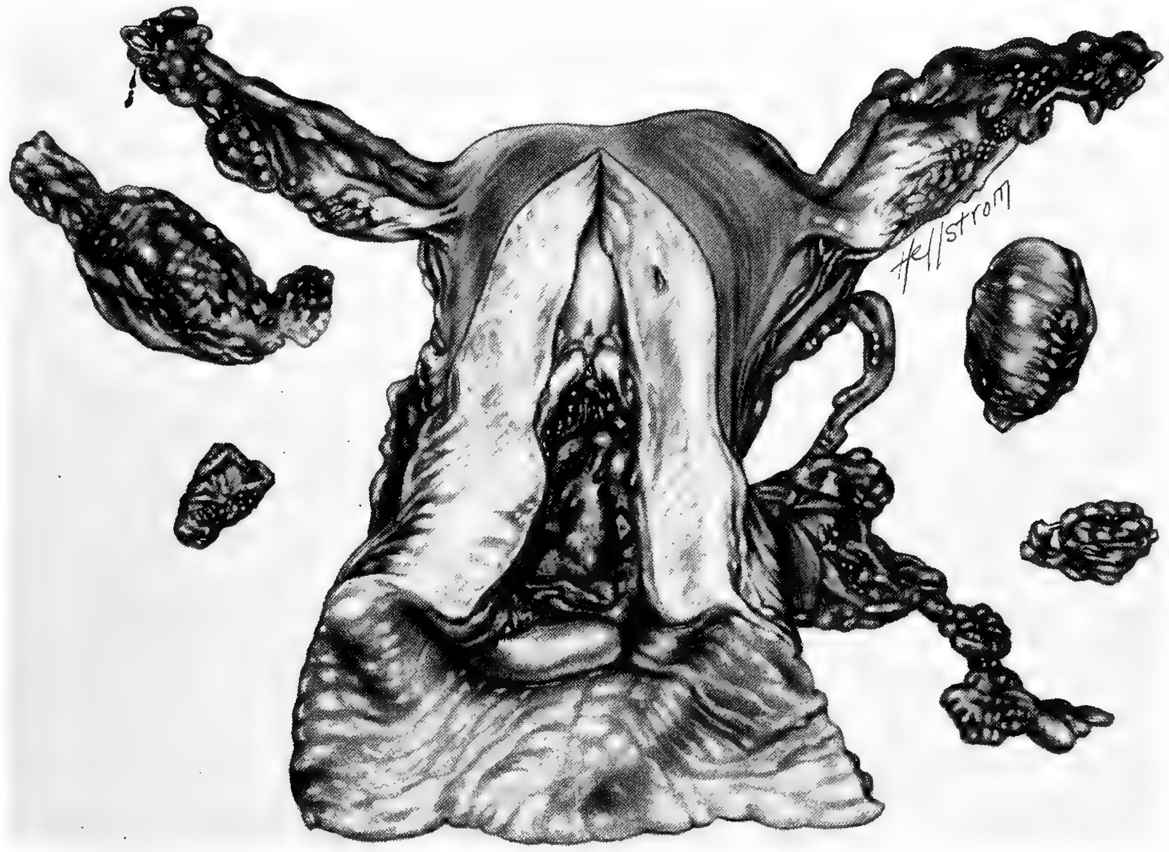


Fig. 94. Squamous cell carcinoma of cervix, clinical stage III, extending up into endometrial cavity and with metastases to lateral lymph nodes. After x-ray therapy and radical excision, cured eight years.

This again suggests that sexual relations is an important factor. Certainly there is no evidence that estrogenic or other hormones have a causal relationship to carcinoma of the cervix. Another point of interest is the relation of trichomonas vaginalis, especially to carcinoma-in-situ. Certainly, marked atypical cells in the cervical smear appear much more commonly in patients with trichomonas vaginalis infections. While trichomonas vaginalis infections are extremely frequently associated with carcinoma-in-situ in ward patients, the association is not obvious in private patients. Some feel that trichomonas vaginalis vaginitis is venereal or related to sexual intercourse, and perhaps it is in many instances, but certainly not in many others. The figures are not available as to the incidence of trichomonas infection in cases with invasive carcinoma of the cervix. Because of the tumor, when present, frequent hemorrhage, and obvious secondary bacterial infection, search is rarely made for the little trichomonas. That bacteria and viruses also may be related is not beyond reason.

The symptoms of carcinoma of the cervix are *none* in the early stages. Bleeding, pain, fistula formation and cachexia indicate advanced cancer. This disease apparently begins as carcinoma-in-situ in the majority of cases (though some may begin as direct invasion, the "spray carcinoma" of Schiller), which has no symptoms, cannot be diagnosed by its gross appearance, except as a possible diagnosis when leukoplakia is seen. There are no symptoms in the early stage of invasive

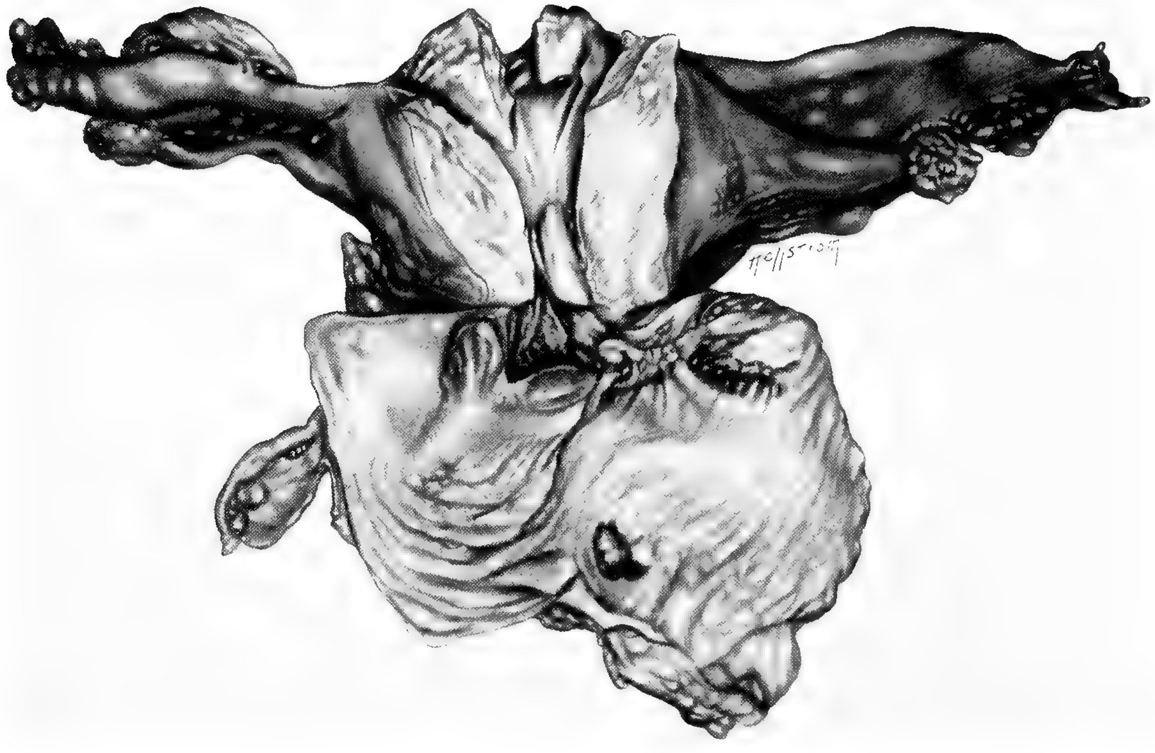


Fig. 95. Squamous cell carcinoma of cervix, recurrent after full x-ray and radium therapy. Extension to parametria and metastases to nodes. After radical excision, had recurrence in six months, followed by death. Lymph nodes are not shown.

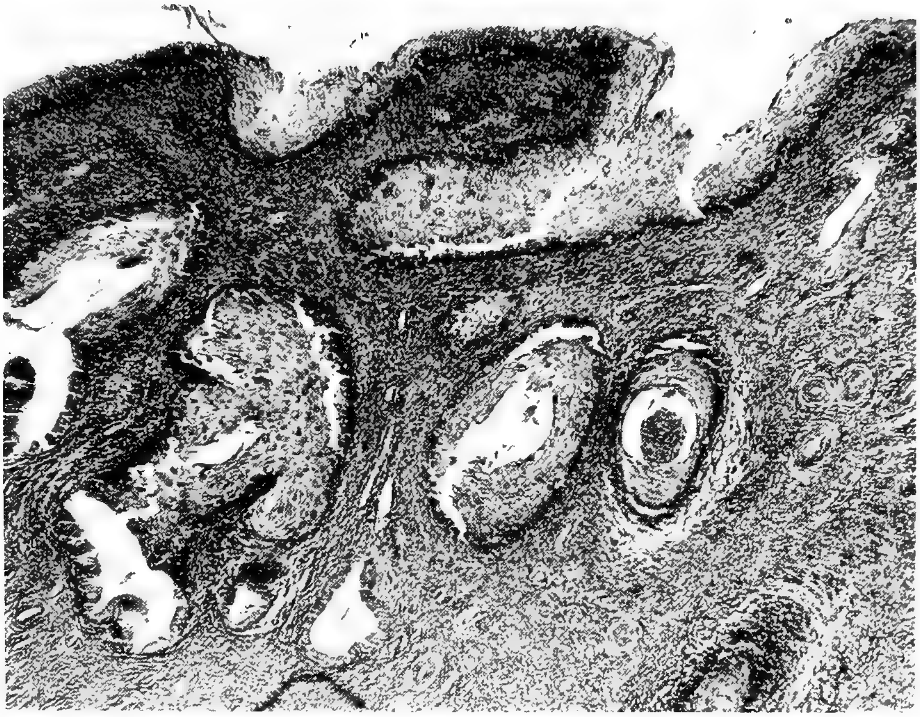


Fig. 96. Squamous cell carcinoma of the cervix of a very cornified type. These individual cells are relatively large, pale and are forming large epithelial pearls.

carcinoma. As the tumor begins to grow, with its great multiplication of cells, a small tumor mass appears on the cervix. When it is only one or two cm. in diameter, it may or may not slough out in the center to form an ulcer with open capillaries and arterioles that may bleed into the vagina. This bleeding especially may occur following sexual intercourse, so that *bleeding after intercourse* is considered one of the most serious of all symptoms that a woman may have. It is remarkable sometimes how a large growth may form without any bleeding. The mass may develop to the size of one's fist, with cauliflower characteristics, quite nodular, granular feeling, and yet unassociated with bleeding. This is rare, to be sure, but it does occur. As a rule, the bleeding later becomes more profuse, severe anemia develops and repeated packing of the vagina at frequent intervals may be necessary to staunch the blood loss. A relatively early symptom is frequency of urination, pointed out some years ago by Henriksen, but this is never diagnostic, nor even a matter to raise suspicion, because frequency of urination occurs so commonly in women. When any degree of pain develops in the pelvis as a result of carcinoma of the cervix, usually there has been extension of the tumor outside the cervix to the lateral walls of the pelvis, so that the chance of cure is greatly diminished. It is generally believed, when the tumor is well-formed and grossly recognizable, that the lesion will cause death of the patient within an average period of fourteen months, if untreated. There are always exceptions, and a small percentage are so slowly growing as to take years to kill the patient. Still others grow like wild-fire and become fatal in a few months. As the tumor extends, pain is a serious problem, requiring narcotics, sometimes requiring cordotomy, alcohol injections in the spinal canal (this is in less favor today), or cobra venom, which some have found of value. The lesion may grow into the bladder, producing symptoms of marked cystitis, and erode the base of the bladder, with the formation of a vesicovaginal

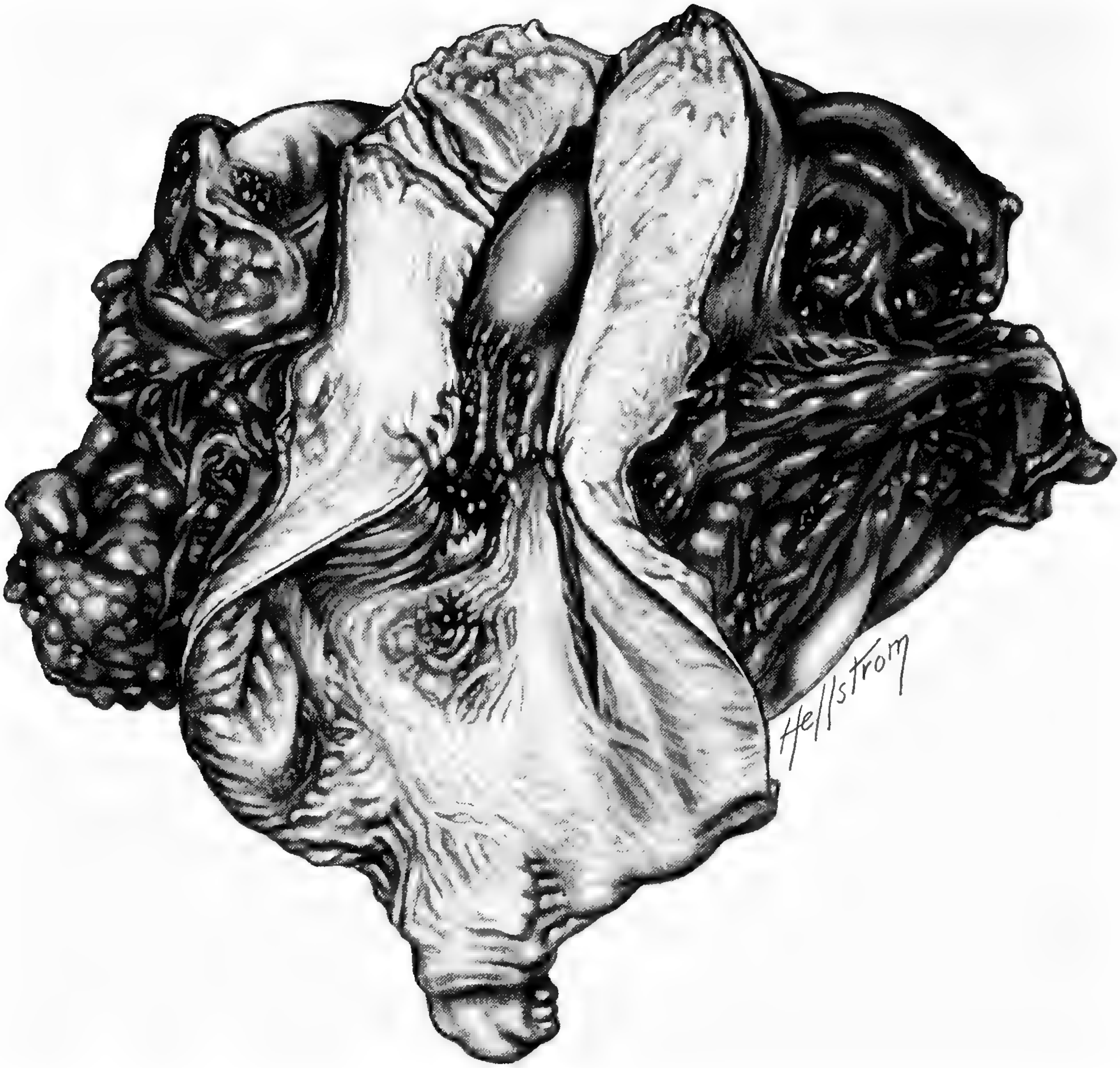


Fig. 97. Squamous cell carcinoma of the cervix, clinical Stage I, recurrent locally and in parametrium after full irradiation therapy, retreated without improvement. After radical excision had recurrence and death.

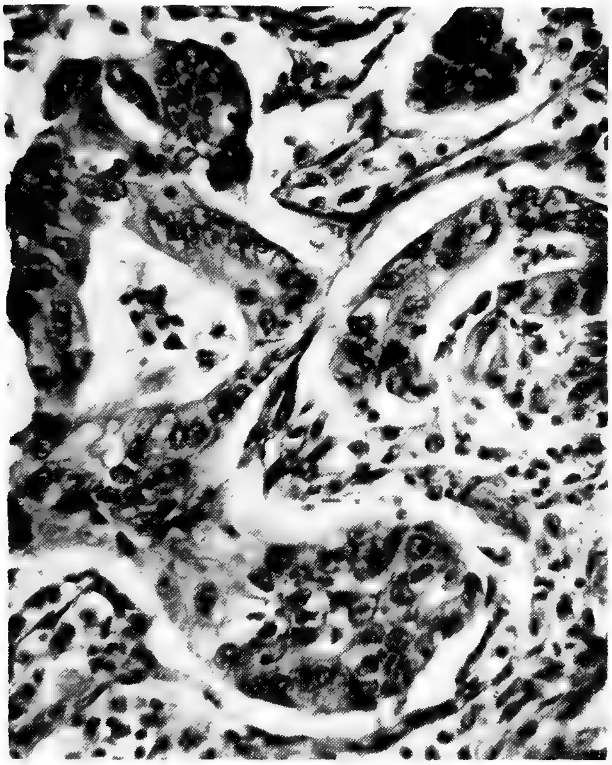


Fig. 98. Adenocarcinoma of the cervix. The glandular form is obvious, the piling up of the cells of two, three and four layers thick, and the marked variations in the size and shape of the nuclei, are characteristic of this quite malignant tumor. In a case with lower grade of malignancy there are more adult-appearing glands, with less piling up and irregularity in the cells. This tumor recurred rapidly after apparent total excision.

fistula. The growth similarly may extend into the rectum, causing diarrhea, tenesmus, bleeding, ulceration and fistula formation. As these changes proceed, the patient becomes increasingly cachectic, anemic from both blood loss and toxemia, and the ureters are constricted by the growth of the tumor, causing hydroureter, hydronephrosis and thinning of the kidney cortex and signs of uremia. Metastases outside the pelvis occur less commonly; in fact, half the patients who die do not have metastases above the pelvic brim. A small percentage do metastasize to the colon, the lymph nodes along the aorta, the liver, the lungs, the brain, the spine, pelvic and other bones. Symptoms occur with these metastases according to their distribution. Cachexia, uremia, and hemorrhage are causes of death.

The treatment of carcinoma of the cervix after it is well formed is not satisfactory. In earlier centuries, cautery was used. Attempts were made to amputate the cervix. Then, in 1818, vaginal hysterectomy was performed successfully for the first time by Langenbeck, especially for the treatment of carcinoma of the cervix, and many were performed after that time, but nearly one hundred years later, it was clear that only ten or fifteen per cent of cases were cured by this method (Clark). Shortly before the turn of the century abdominal total hysterectomy was developed (1878). As aseptic technique was adopted more widely, this operation was extended for carcinoma of the cervix. Wertheim of Germany, later Victor Bonney of England, and today Meigs of Boston, are indelibly associated with radical hysterectomy, with its selective lymph node excision by Wertheim, and the thorough and routine lymph node excision by Meigs.

In earlier years, especially because of the high primary mortality, due to blood loss, infection and imperfect anesthesia, Kelly and Burnam, and others, substituted radium therapy in 1912. Many of the cases showed dramatic recovery, with disappearance of the tumor, and apparent cure. It is obvious why those earlier workers had such great enthusiasm for cure of all cases, often thinking a larger and larger amount of irradiation was the answer. It soon became clear that the cure rate was about twenty per cent of the total, and in the next twenty or thirty years this cure rate extended to about twenty-five per cent. Today it is about forty per cent of all cases seen (the figure will vary, depending on the number of early cases found). This low cure rate continues because of the relatively large number of advanced tumors, especially in the charity services. Tumors of Stage III and IV develop due to delay in diagnosis, because the patient fears to present herself, and less often the physician delays examination or fails to recognize the lesion. These advanced cases have kept the over-all rate of cure at the present low figure.

It appears that in Stage I cases as many may be cured by radical hysterectomy with pelvic node dissection as by irradiation therapy, in each instance from sixty to seventy to eighty per cent of cases. Radical surgery requires great effort, team work, multiple transfusions, and is associated with unhappy complications in many cases. Fistulas of the ureter or bladder have been reported in eight to ten per cent. Unless complications, particularly fistulas, can be avoided, the operation will never be favored completely.

The more standard treatment today is that of irradiation therapy, including radium, x-ray and cobalt. Irradiation therapy, if carefully given, both by external means and local application against the tumor, has less immediate risk, requires much less effort in relation to the prolonged operative procedures, but again is associated with complications of its own. Fistulas are less common than with radical surgery, but remain a worrysome problem. Effects on the bladder and bowel may be obvious, acute and severe, and may be delayed for several years, with subsequent bowel necrosis, fistula formation, obstruction, chronic diarrhea and chronic bowel symptoms. Ureteral obstruction may occur due to irradiation scarring, and residual tumor often is found trapped in the irradiation fibrosis. Irradiation scarring alone may cause much of the ureteral obstruction. A surprising number of patients develop pathological fractures of the neck of the femur, and occasionally of the ischium and pubic bones. These fractures may occur several years after intensive therapy for carcinoma of the cervix. The vagina tends to become quite atrophic, shrunken, inflamed, sealed with adhesions, and impossible for sexual relations, despite douches, daily dilatations with candles, and the like. Irradiation vaginitis may be difficult to relieve. Degrees of weakness, especially in the legs, may follow irradiation therapy, persisting for months or years.

The occurrence of these complications of surgical or irradiation therapy has been a necessary evil for the chance of cure of this lethal disease. It does mean that neither method is entirely satisfactory as a treatment today. In the Stage II and III cases, radical hysterectomy and pelvic node dissection is rarely indicated. In these Stages II and III, a smaller percentage may be cured by irradiation therapy, provided the tumor is sensitive. One can only hope for such sensitivity. Stage IV carcinoma, with invasion of the rectum and bladder and intense induration through the pelvis, is seldom cured in any patients by irradiation therapy. If any are cured, it is a great rarity. In these and in the Stage III cases, pelvic evisceration or eventration, according to the method of Brunschwig may be attempted. Brunschwig has obtained some good results with five year "cures" in twenty per cent of patients, a twenty per cent that would have been surely lost. While Brunschwig has used wet colostomy, transplanting the ureters into the descending colon, Bricker has developed the ileal pouch, placing the ureters into an isolated segment of ileum, and allowing the urine to drain out of a separate opening into a rubber or plastic bag. Bricker, Parsons, and others, also have had extraordinary results in the cure of advanced carcinoma by super-radical surgery. These efforts are definitely worthwhile and are to be commended, particularly for the patient who understands and is willing to accept such treatment.

A point of great interest at present is the research of Graham and Graham on "sensitivity response (SR)," and "radiation response (RR)." These investigators believe that the appearance and response of the normal squamous epithelial cells, seen in the smear of the patient with cancer of the cervix, yield a clue to radiation curability in that case. They attempt to separate the

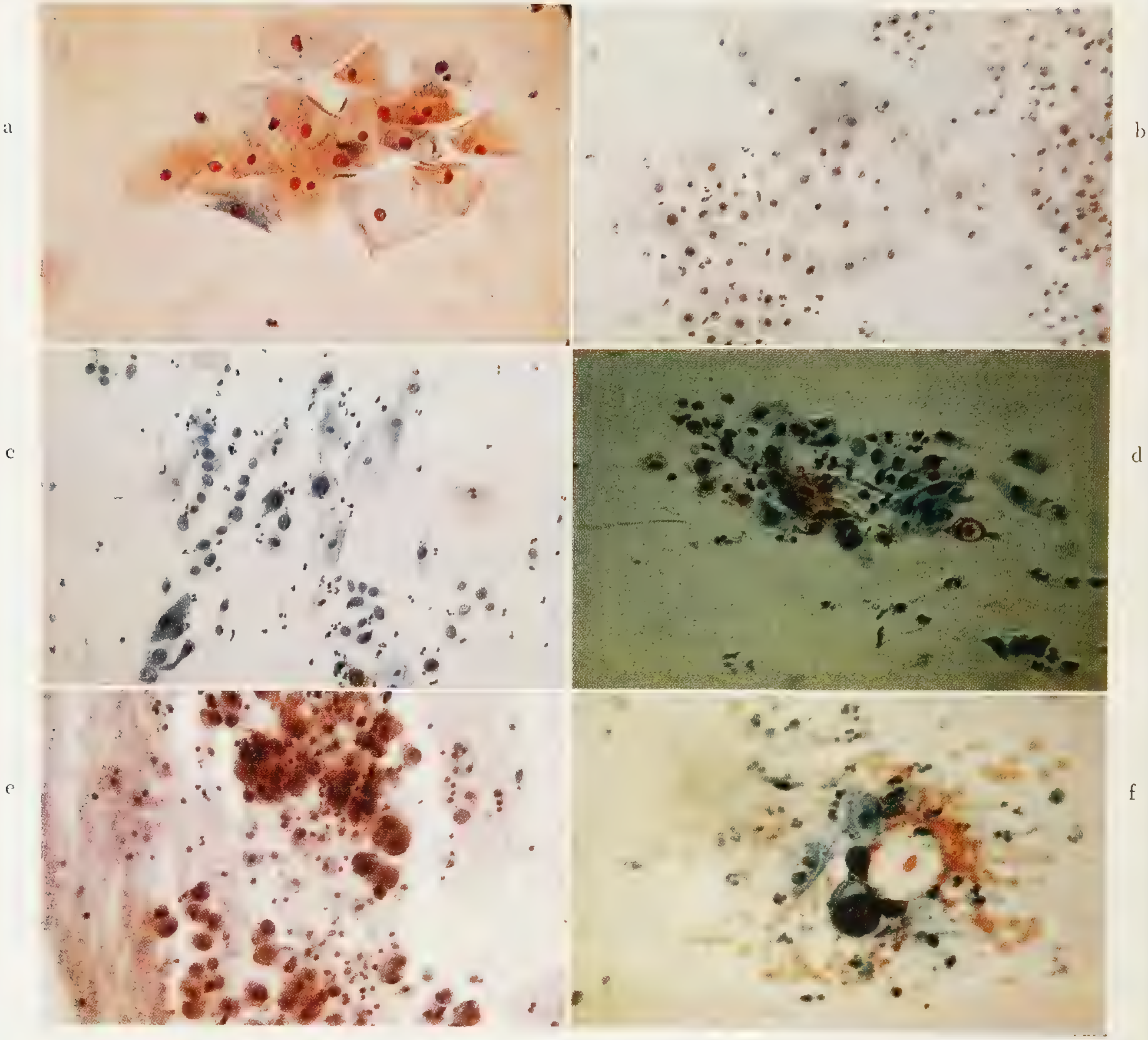


PLATE III

a. Normal superficial cells shed in the vagina, indicating a strong estrogenic effect. The cells are hexagonal, large, with small round nuclei. The blue stain indicated precornified cells, while the pink stain indicates full cornification. The proportions of these cells vary during the menstrual cycle, and indicate finer shades of difference in amounts of estrogenic hormone present.

b. Normal post-menopausal cells. Basal and parabasal cells, with round and oval nuclei, and some pyknosis and degeneration. Nuclei make up much less than fifty-per cent of size of cells.

c. Dysplasia. More variation in cell type and size. Not sufficiently hyperchromatic or large enough nuclei for carcinoma.

d. Pregnancy and dysplasia. Moderate cornification. Nuclei vary greatly in size and shape, with pyknosis, intranuclear oedema and multinucleation. This is suspicious of carcinoma, but the presence of pregnancy may enhance the changes.

e. Invasive carcinoma of the cervix. Hyperchromatic, nuclei, multinucleation, macronucleoli. Clumpy and no definite cell border.

f. Adenocarcinoma of endometrium. Hyperchromatic enlarged nuclei, which take up more than half of the cell. Usually vacuolization. Clustering together.

cases that cannot be cured by irradiation therapy and advise the surgical approach in those. If more than ten per cent of the normal basal cells in the smear have increased density in the cytoplasm and vacuoles in the cytoplasm, the patient has a good SR, and should be sensitive to irradiation. If seventy-five per cent of the normal basal cells become greatly enlarged, with enlarged nucleus, and fine vacuoles in the cytoplasm after irradiation therapy is begun, the patient has a good radiation response, good RR, and may be expected to respond well to this form of treatment. Glucksman has studied repeated biopsies during irradiation therapy and believes that mitotic counts and cellular changes may aid in determining irradiation sensitivity. Sensitivity does not necessarily mean curability. In many instances the tumor may shrink extraordinarily rapidly with x-ray and radium, apparently being very sensitive, only to recur rapidly with a fatal result.

The application of radium and external irradiation therapy make up the most widely accepted treatment of carcinoma of the cervix in this country. With careful determination of dosage to the tumor, to point A (2 cm. lateral to the cervix at the level of the ureter and uterine artery), and to the node areas along the hypogastric vessels, in the obturator foramen and along the external iliac vessels, with some degree of mathematical accuracy, with the avoidance of overdosage of the normal organs, encouraging results are obtained. Until the cause and prevention of cancer can be found, the best results will follow the finding of earlier and earlier cases. If all in-situ cases are found and treated carefully, perhaps the disease may almost disappear.

CYTOLOGY

The history and development of cytology in these recent years are mainly related to the discoveries of one individual, G. N. Papanicalaou, Professor of Anatomy at Cornell Medical School. For twenty-five years or longer, Doctor Papanicolaou followed the vaginal smears of mice, rats and other experimental animals to determine the estrogenic variations in the reproductive cycles. Gradually, this study of the hormone effects on the desquamated vaginal epithelium was extended to the human. In the course of these years, Papanicolaou observed abnormal cells at increasingly frequent intervals and determined to his satisfaction that they may indicate carcinoma. His first paper on the diagnosis of cancer by means of the vaginal smear appeared in 1941. The classic monograph "Diagnosis of Uterine Cancer by the Vaginal Smear" by Papincolaou and Trout, published by the Commonwealth Fund in 1943, presented the basis of this now recognized extremely important laboratory aid for the diagnosis of cancer and precancer in women.

Following World War II, interest developed in many medical centers to study this method further, but the pathologists in general were slow to accept the method. In the next several years, disagreements arose as to the accuracy of the method, and the expense involved, and some outstanding medical centers discontinued use of the Papanicolaou smear. Novak particularly, was hesitant to accept the vaginal smear, not only for diagnosis but as a worth-while screening procedure.

In more recent years, cervical cytology has been widely acclaimed as a screening technique for large numbers of women, to isolate those with suspicious cells for further study. While great care must be exercised in evaluation of the findings in cervical smear examination, yet there is increasing confidence in the diagnostic possibilities of the test. At present, always tissue examination is required for confirmation.

Certain centers particularly have pressed forward in this field. Graham at Harvard and later at Roswell Park, Cuyler at Duke, Dockerty at the Mayo Clinic, and a number of others have made most significant contributions in the application and interpretation of cytology. Recently, Reagan at Western Reserve, Eriksen at Tennessee, Christopherson at Louisville, and other pathologists have had extensive experience in the interpretation of cervical cytology, and by correlation with repeated biopsies and careful follow-up of the patients, are differentiating the dysplasias, carcinoma-in-situ, and the invasive carcinomas with increasing accuracy. Great impetus for the routine use of cervical cytology has been induced by the Public Health Grants for mass screening, at Memphis, Louisville, and other centers. The demonstration of the accuracy of the method and the findings in a large sample of the population have been quite important in establishing the necessity of routine cytologic studies.

Now it is evident that this test is accurate to discover early carcinoma or carcinoma-in-situ of the cervix in ninety-six or ninety-eight per cent of the cases, but in only forty per cent of cases with endometrical carcinoma. It is also evident that this test should be performed once yearly on each woman after the age of twenty years.

The method of taking the smears has been mentioned in chapter one. It consists basically of taking two smears, preferably when the patient is not menstruating (but it is not to be delayed because of abnormal bleeding), and preferably without douching. A dry clean speculum is inserted to expose the cervix. A small swab tipped with non-absorbent cotton is introduced into the cervical canal, rotated, removed and rolled on the clean slide which is immediately placed in the fixing solution. They the Ayre wooden spatula is rotated around the cervical os and smeared on the second slide. This, also, is immediately placed in the fixative, before drying of the slide. After fixation for at least thirty minutes in a solution of equal parts ninety-five per cent alcohol and ether, or in ninety-five per cent alcohol alone, the slides are stained. The most widely used stain is the multiple dye application of Papanicolaou. Many modifications using different dyes, silver, and fluorescent chemicals, have been used, with individual preferences.

The availability of this method depends on the screener and the cytologist. The technician at the screening level can examine a large number of slides and mark those with suspicious cells. The cytologist, if a technician, may further eliminate and demarcate the individual slides. Finally, the pathologist may pass on the diagnostic criteria of the cells. The accuracy of the scanner and cytologist is impressive. The pathologist must learn a new approach to the diagnosis of the individual cells, which appear dissimilar from those seen in the tissue sections.

The characteristics of the cells found in different situations and pathological conditions are becoming more distinctive. In the normal squamous cells that are shed from the cervix and vagina, the shape of the nuclei are round or oval, the borders are clear and regular, and there is only slight variation in chromatin content. The cytoplasm may be flat, wrinkled, or folded, and may or may not contain glycogen.

After the menopause, the basal and para-basal cells show vesicular or finely granular nuclei, degrees of pyknosis, and distinct borders. The cytoplasm is thin and transparent. Reserve cells are round, have a foamy-like cytoplasm, and the cell border is prominent. Endocervical cells may form in a palisade, have eccentric nuclei and brush borders.

In dysplasia, there occur large polyhedral cells, multinucleated cells, hyperchromatic nuclei, but not hyperchromatic enough or large enough for carcinoma. There is increased variation in cell size and type.

In carcinoma-in-situ, the cells have a similar appearance. The nuclei make up more than fifty per cent of the cell. They are round and oval, hyperchromatic and clumpy, and the borders are irregular. Multinucleation occurs commonly, and the cells do not adhere to one another.

With invasive squamous cell carcinoma, there is no definite cell border. The nuclei are hyperchromatic, with clumping, macronucleoli and multinucleation.

In adenocarcinoma of the endometrium, clustering of cells, vacuolization, and occasional multinucleation are found. The nuclei are hyperchromatic and make up more than fifty per cent of the cells.

The microscopic cellular changes that make up the science of cytology are not so quickly and easily learned. A wide experience and long hours of effort are necessary to accurately differentiate these cells.

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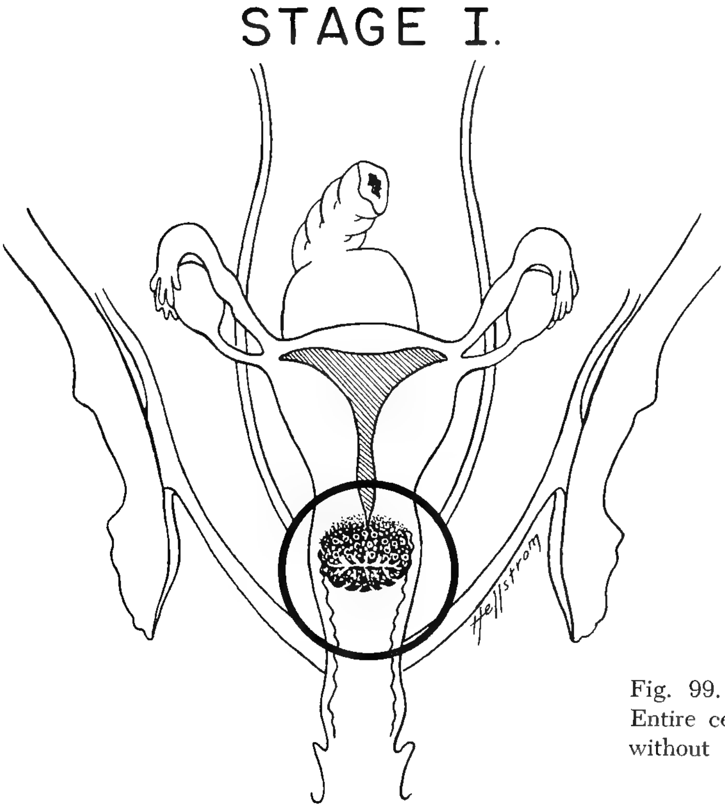


Fig. 99. Carcinoma, cervix uteri, clinical Stage I. Entire cervix involved with firm ulcerative growth without enlargement.

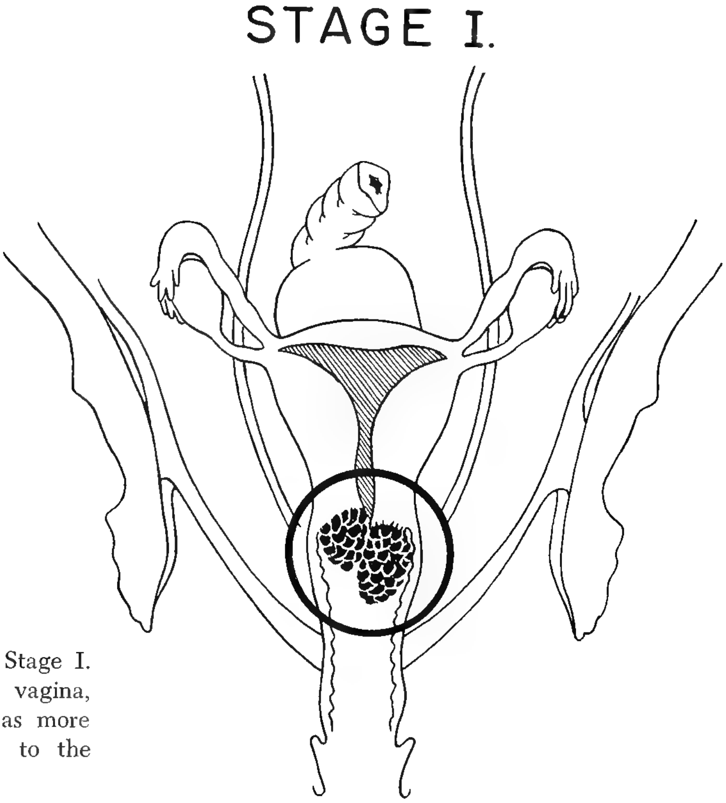


Fig. 100. Carcinoma, cervix uteri, clinical Stage I. The lesion is exophytic, protruding into the vagina, involving entire cervix. Considered by some as more radio-sensitive in this form. Grossly limited to the cervix.

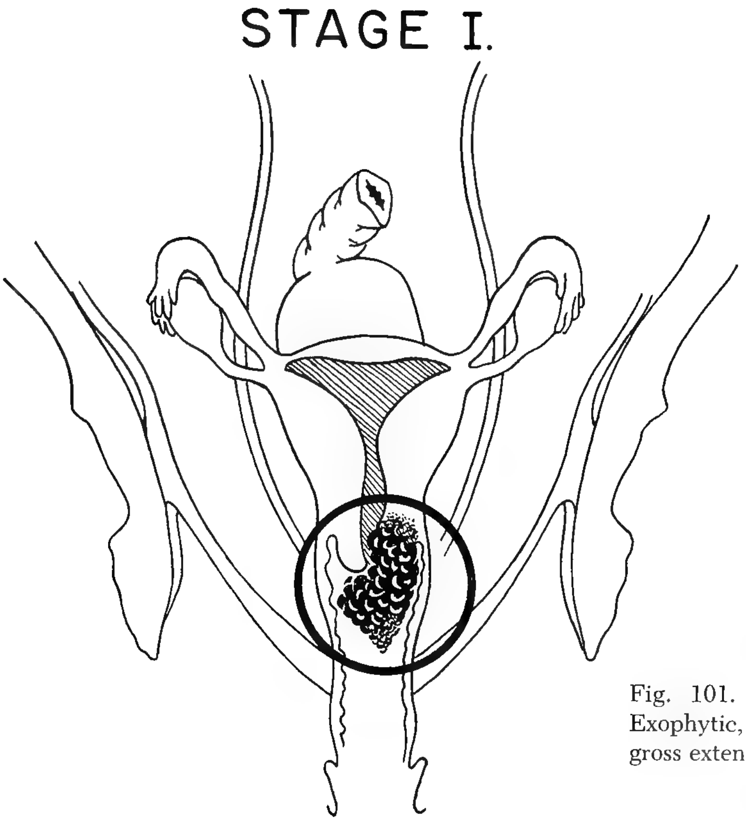


Fig. 101. Carcinoma, cervix uteri, clinical Stage I. Exophytic, involving one lip, quite obvious, with no gross extension to vagina or parametrium.

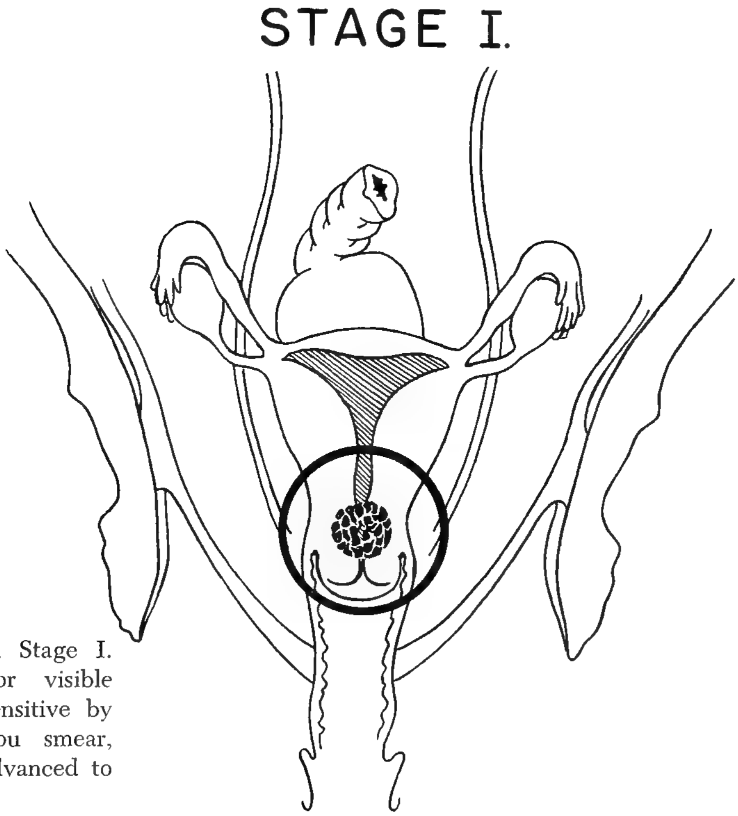


Fig. 102. Carcinoma, cervix uteri, clinical Stage I. Completely endocervical, no palpable or visible lesion. Endophytic, considered less radio-sensitive by some observers. Detected by Papanicolaou smear, or curettage and biopsy after sufficiently advanced to cause bleeding.

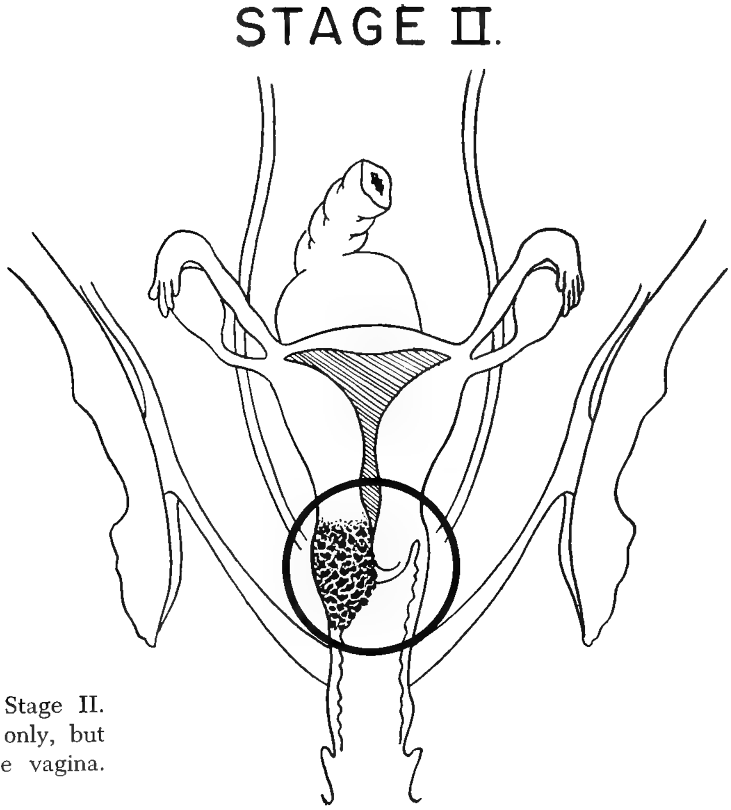


Fig. 103. Carcinoma, cervix uteri, clinical Stage II. The tumor involves one side of the cervix only, but extends down onto the upper third of the vagina. No induration in the parametrium.

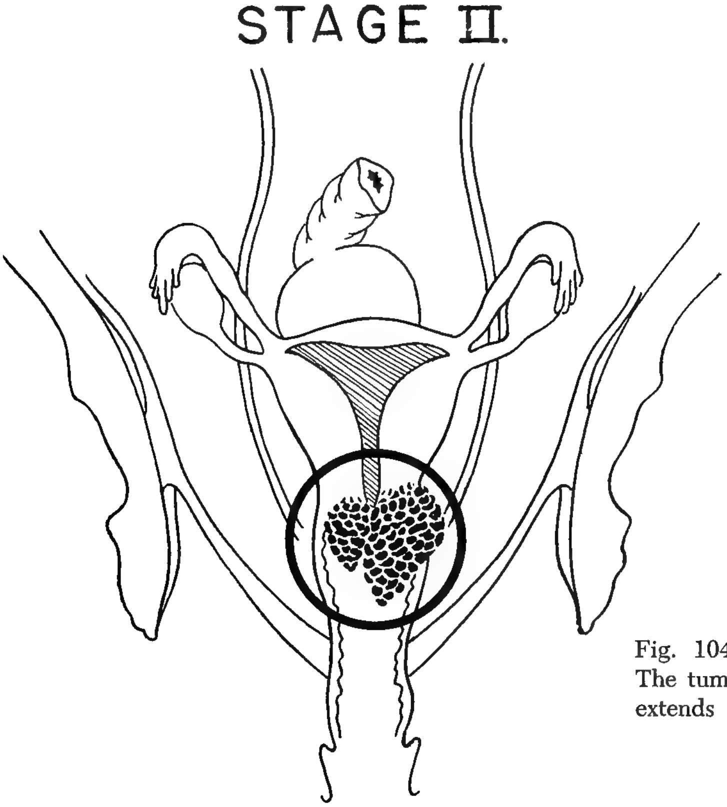


Fig. 104. Carcinoma, cervix uteri, clinical Stage II. The tumor involves the entire cervix, is exophytic, but extends slightly into the parametrium on one side.

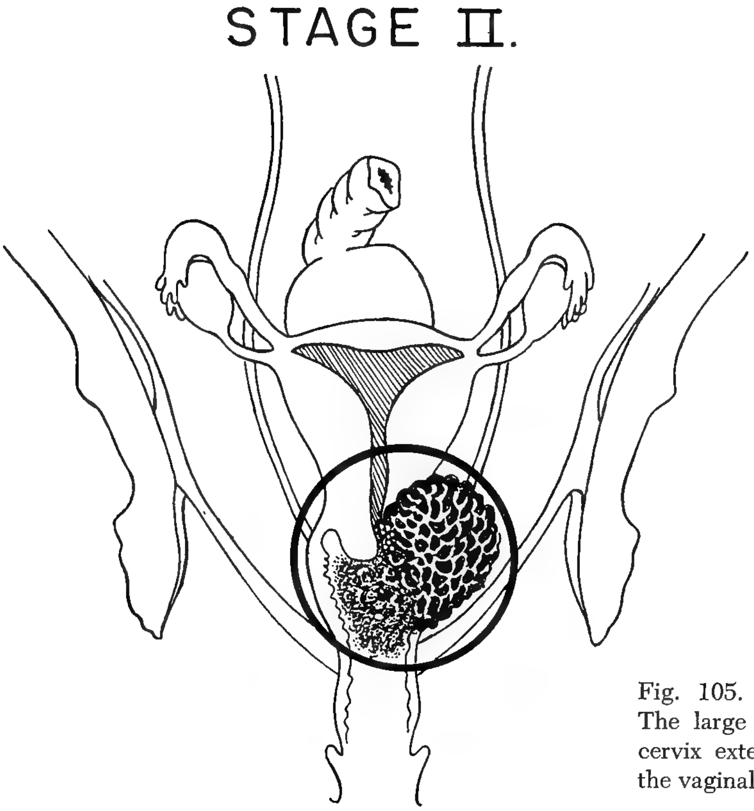


Fig. 105. Carcinoma, cervix uteri, clinical Stage II. The large exophytic tumor involving one side of the cervix extends well into the parametrium, but not to the vaginal wall.

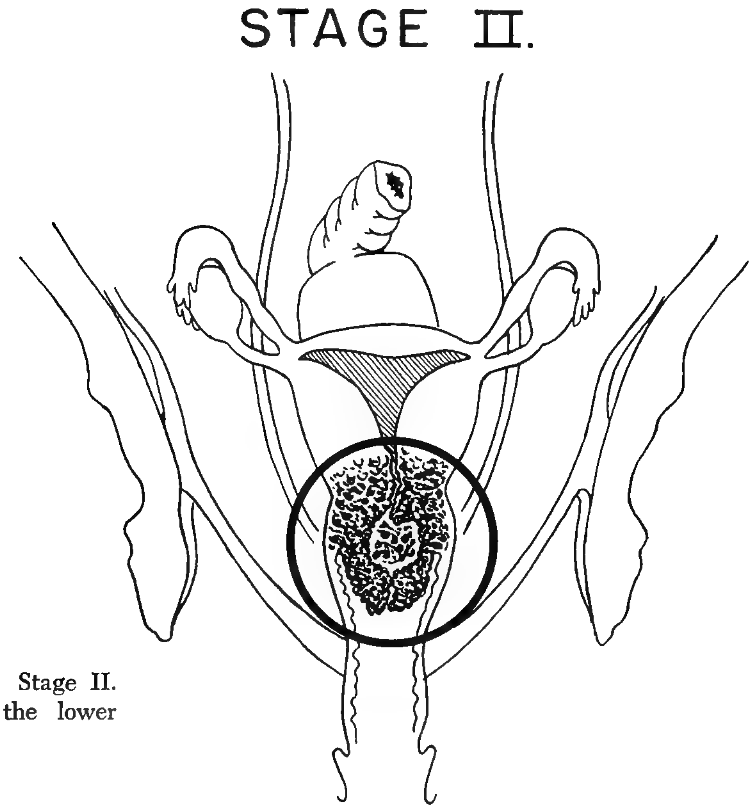


Fig. 106. Carcinoma, cervix uteri, clinical Stage II. The entire cervix is involved, but also the lower portion of the myometrium.

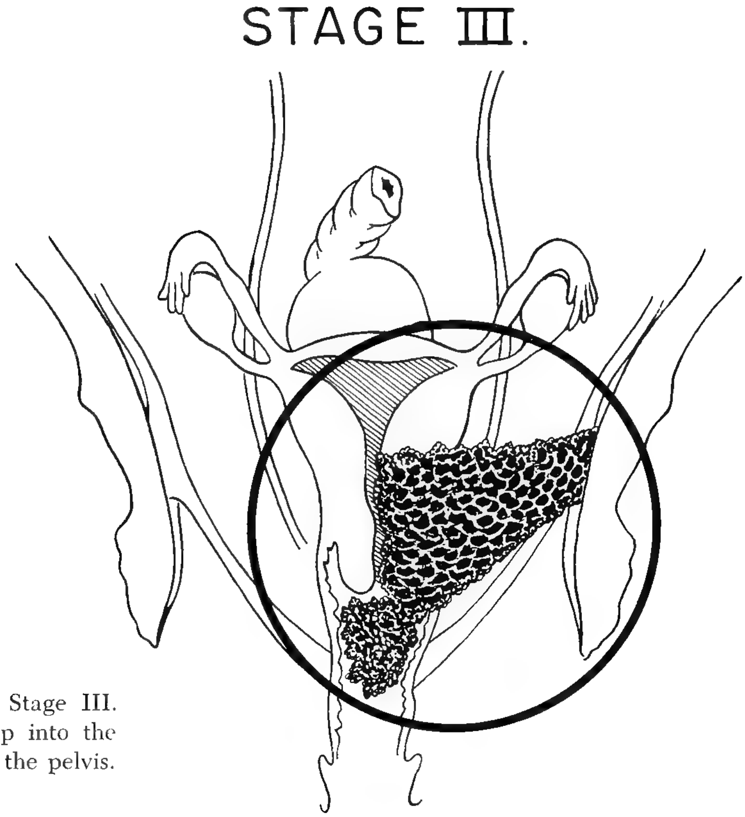


Fig. 107. Carcinoma, cervix uteri, clinical Stage III. The lesion has extended from the cervix up into the endometrial cavity, and also to the walls of the pelvis.

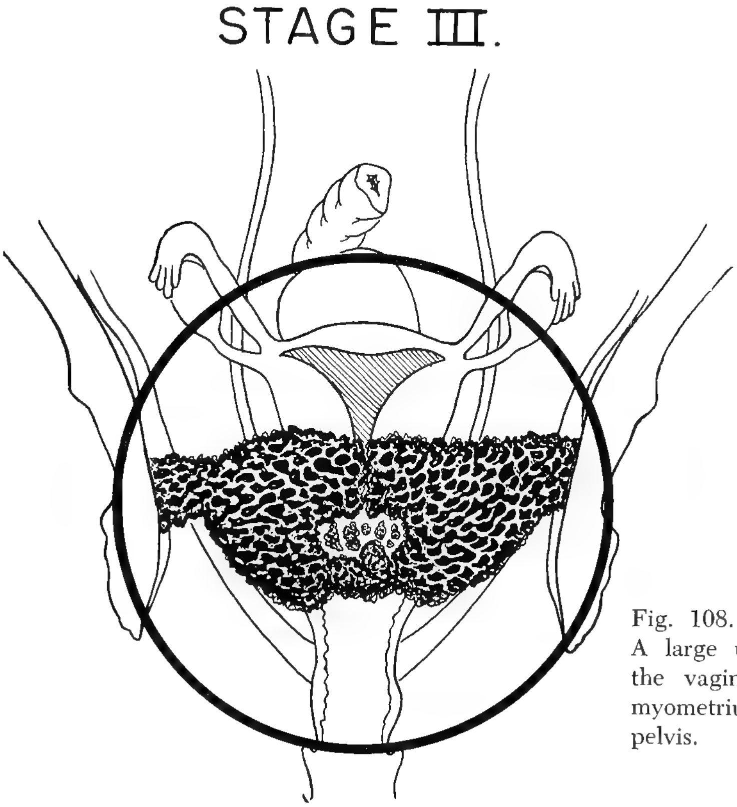


Fig. 108. Carcinoma cervix uteri, clinical Stage III. A large ulcerative lesion, which has extended onto the vaginal wall, up into the endometrium and myometrium, and out to each side wall of the bony pelvis.

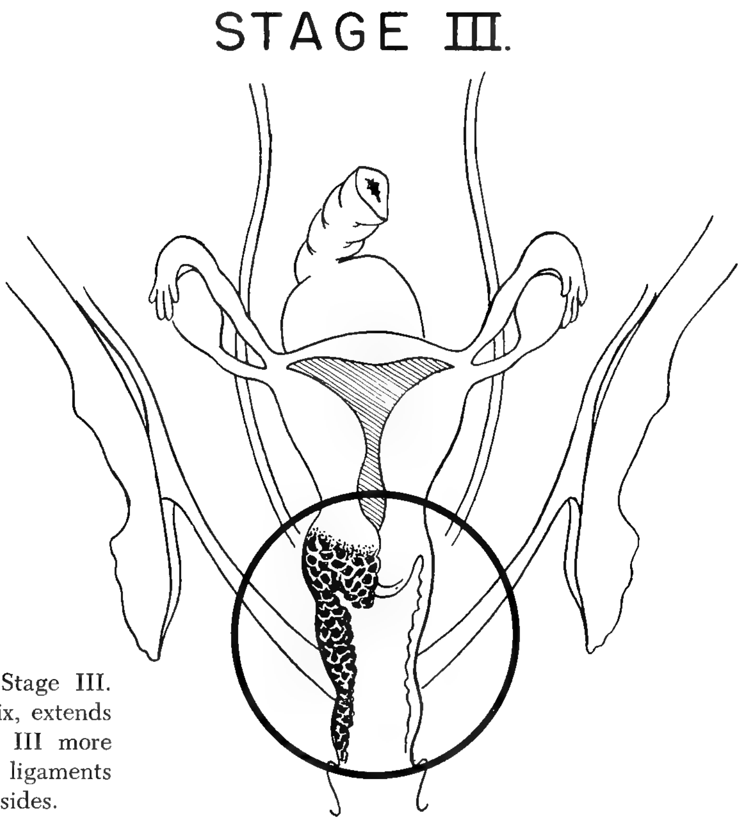


Fig. 109. Carcinoma, cervix uteri, clinical Stage III. The tumor, involving one side of the cervix, extends onto the lower third of the vagina. Stage III more frequently indicates extension in the broad ligaments to the wall of the pelvis, on one or both sides.

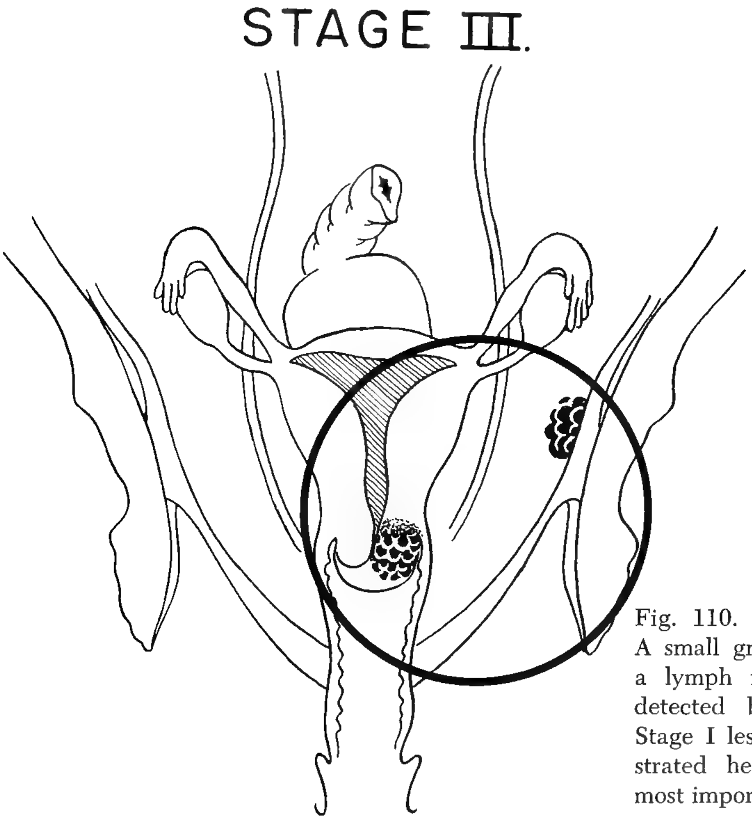


Fig. 110. Carcinoma, cervix uteri, clinical Stage III. A small gross lesion of the cervix, with metastasis to a lymph node at the pelvic wall. This cannot be detected by physical examination. Many apparent Stage I lesions are really Stage III lesions, as demonstrated here. An understanding of this diagram **is** most important.

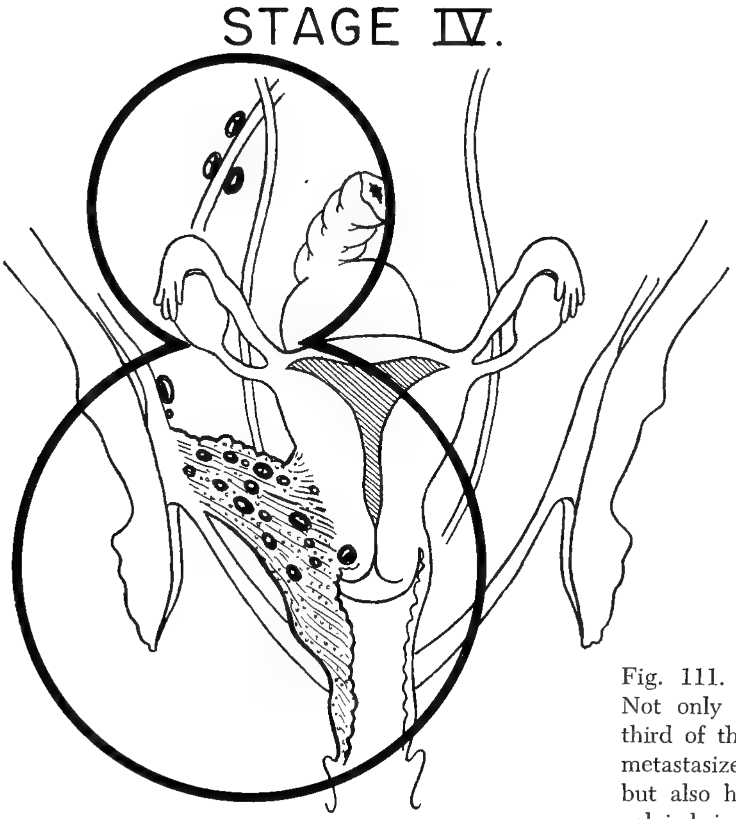


Fig. 111. Carcinoma cervix uteri, clinical Stage IV. Not only has the lesion extended to the lower third of the vagina, to the wall of the pelvis and has metastasized to the pelvic lymph nodes (Stage III), but also has metastasized to lymph nodes above the pelvic brim (Stage IV).

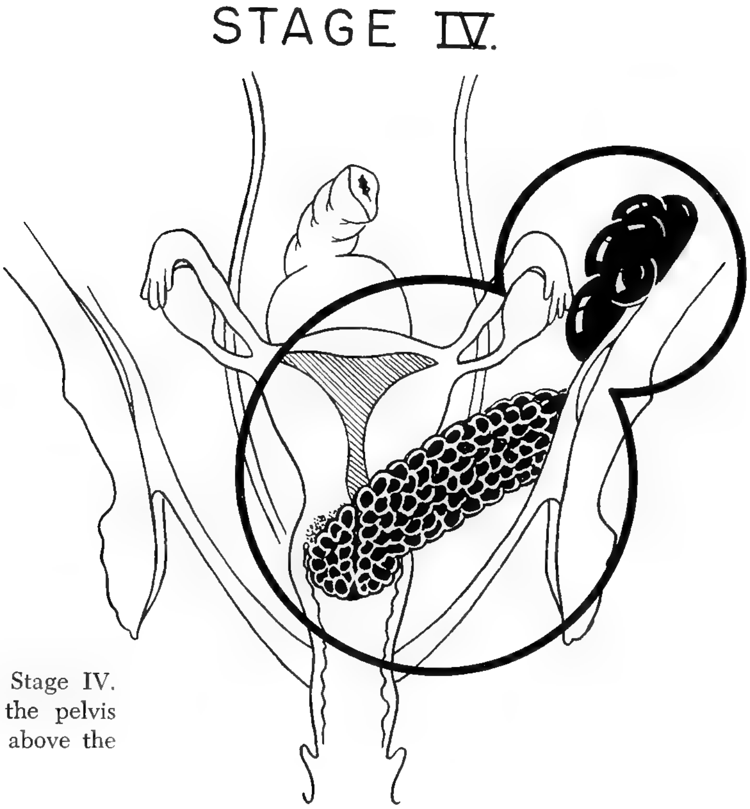


Fig. 112. Carcinoma cervix uteri, clinical Stage IV. The tumor has extended to the wall of the pelvis (Stage III), but also to the lymph nodes above the pelvic brim (Stage IV).

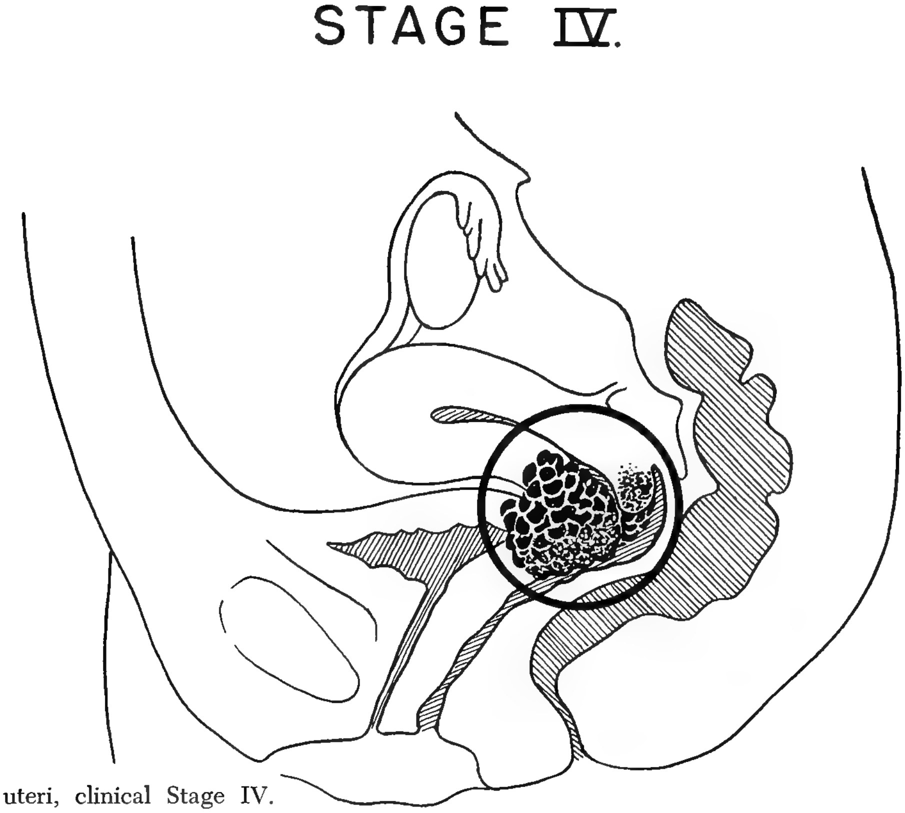


Fig. 113. Carcinoma, cervix uteri, clinical Stage IV. The lesion here has extended into the bladder.

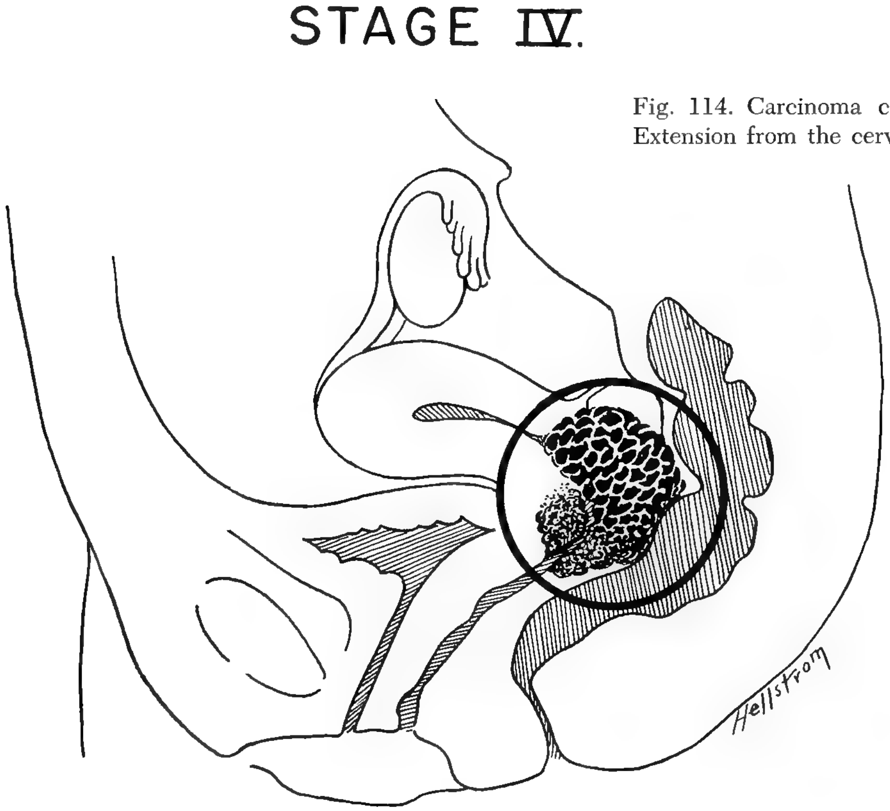


Fig. 114. Carcinoma cervix uteri, clinical Stage IV. Extension from the cervix into the wall of the rectum.

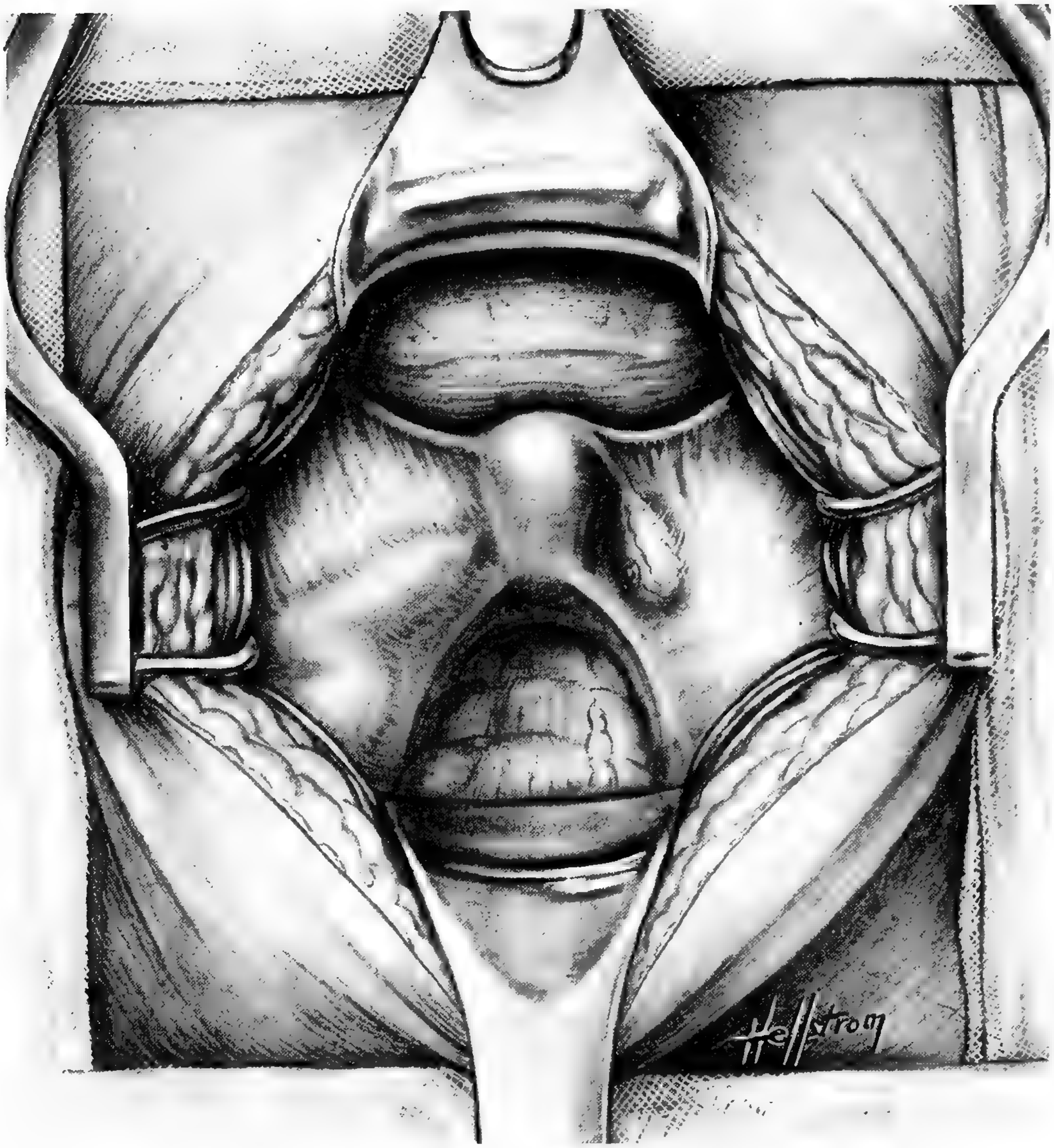


Fig. 115. Late complication from radiation treatment for carcinoma of the cervix. In 1925, both tubes and left ovary were removed. In 1937, she was treated with radium and x-ray therapy for cauliflower carcinoma of the cervix. In 1954 at time of this drawing, patient in uremia. Obliteration of right ureter and kidney. Left hydronephrosis and hydroureter from stricture at point A.

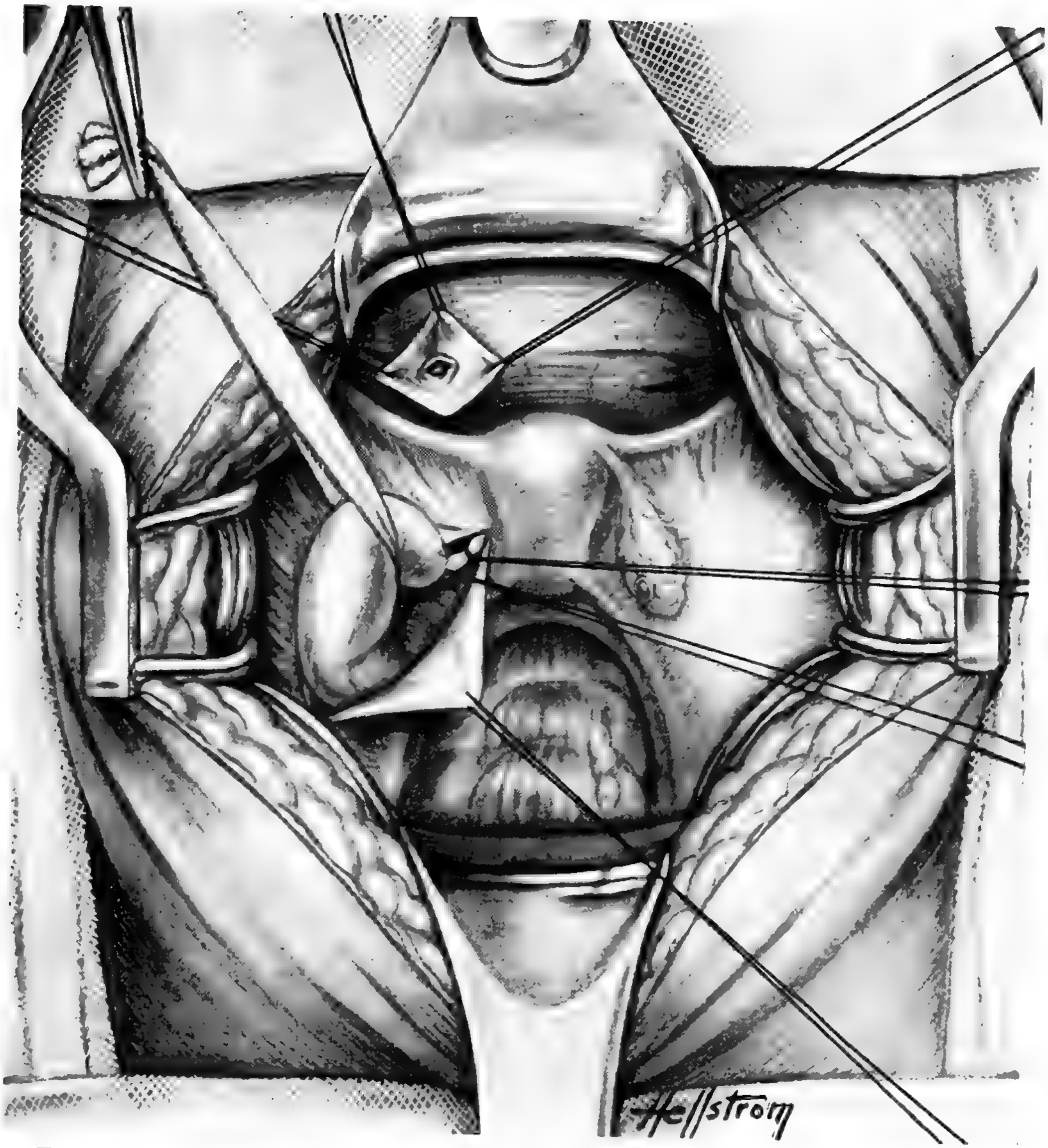


Fig. 116. Left ureter mobilized. Opening made in peritoneum over bladder and in bladder wall.

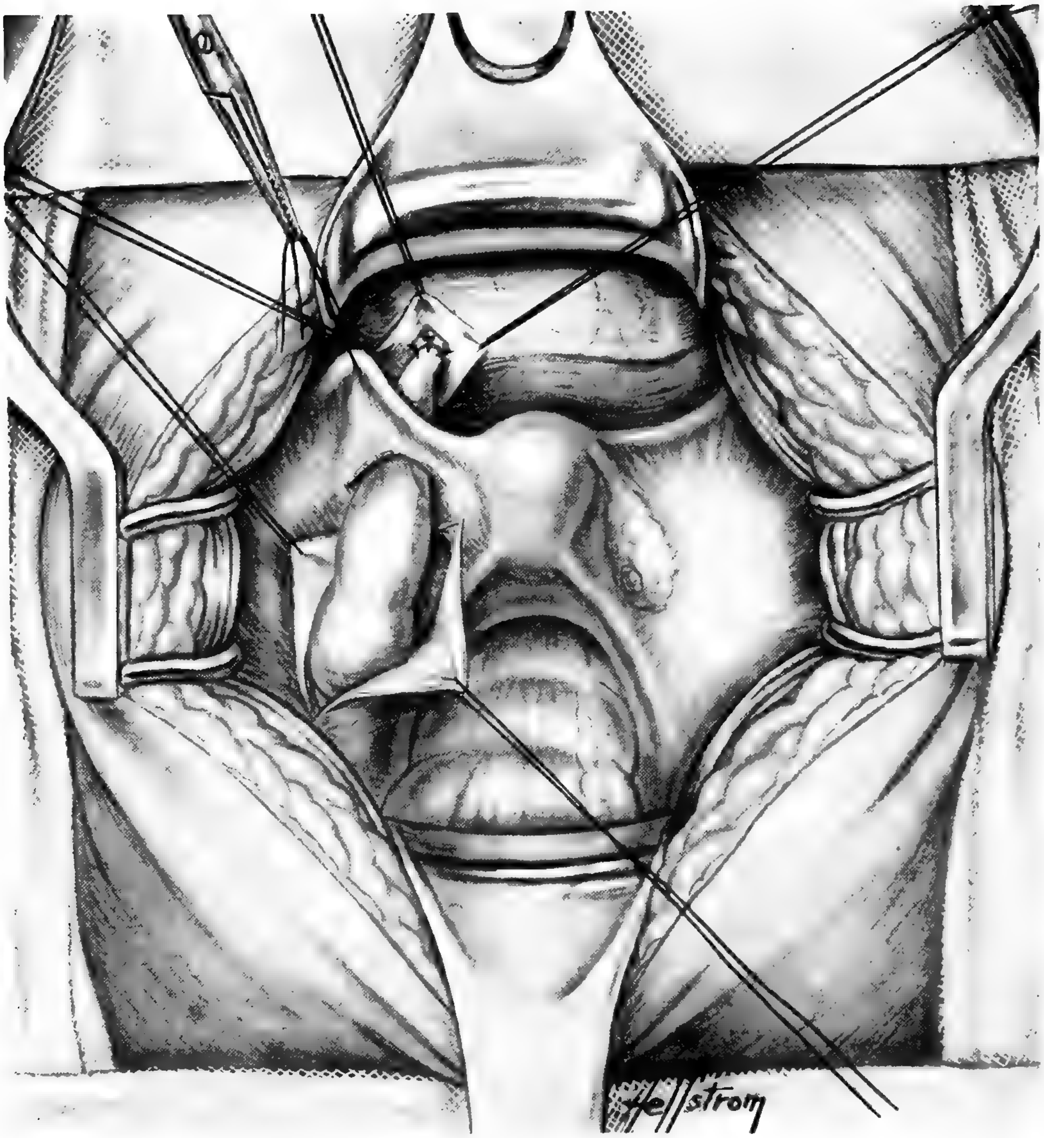


Fig. 117. Ureter brought under round ligament and sutured into bladder, using interrupted fine chromic sutures.

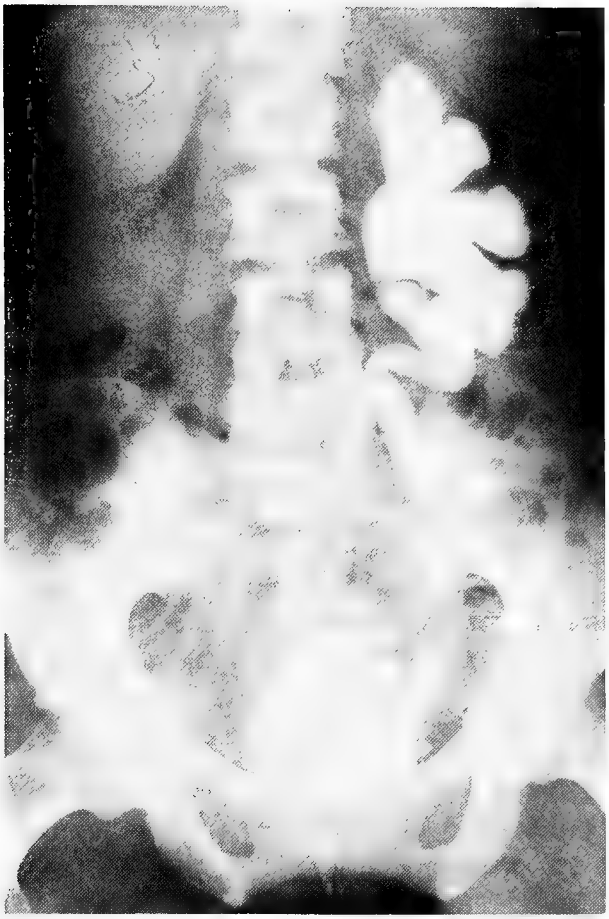


Fig. 118. Postoperative cystogram showing reflux into left ureter and kidney pelvis. The patient improved and lived two years, finally dying of uremia. There was no clinical evidence of recurrent carcinoma over these twenty years.

CHAPTER VI

Endometrium
Menstrual Functions and Dysfunctions – Neoplasms

Menstruation has mystified man from the beginning of time, and regardless of our understanding of complicated hormonal relations today, there remain many unknown facts regarding this process which has played its part in giving each of us existence in this scientific world. Historical notes have been summarized by Novak, and more recently by Fluhman. As Carlson has said, the modern ordinary man knows little more of science than his ancestor of a million years ago. In olden times the appearance of a menstruating woman was considered a cause of the souring of wine, withering of grain, sterility of seeds, and the loss of individual combats and wars. She was said to have caused silver to blacken, ore to disappear in mines, hams to spoil. The cause of menstruation was attributed to gods, evil spirits, animals, reptiles and the moon. Many have stated that menstruation occurred mainly in the phase of the new moon. Menstruation has long been thought to rid the body of poisonous materials, and this belief is held widely at the present time. Galen believed there was a plethora of blood and that this form of blood-letting was necessary for health. In historic times women were isolated in huts during menstruation, and even at present the male feels a little repugnance at the restraints of menstruation, some of which are natural and others imposed by the mistaken philosophers and physicians. Blood itself, from its earliest relation to mortal wounds and slaughter of beasts for protection and sustenance, has brought a psychological wince, especially to the male.

In the nineteenth century, scientific men gradually understood that menstruation is related to ovarian function. Pfluger believed that impulses extended down an ovarian nerve to stimulate menstruation. Our modern concepts of endocrine relationship began in 1908 when Hitschmann and Adler clearly demonstrated the endometrial cyclic changes in the human female. Halban, Fraenkel and Leo Loeb performed fascinating experiments to explain the action of the corpus luteum; Schroeder correlated endometrial and ovarian cycles; the gonatrophic hormone from the anterior lobe of the pituitary gland was found by Evans and Long, Smith and Engle, and Ascheim and Zondek; the estrogenic hormones were isolated by Frank, Allen, Doisy and Butenandt; the corpus luteum hormone was discovered by Corner, W. Allen and Hisaw; and finally Markee demonstrated the menstrual process in endometrial implants in the eyes of monkeys. These and many other remarkable discoveries led us into our present understanding of endometrial and pelvic function in general.

The mucous membrane lining of the uterus is slightly thickened at birth with widely separated but well-formed, slightly curved nonsecretory glands, stimulated by the large amount of estrogen, mainly produced by the foetus' own placenta. But this estrogenic effect, which also causes a growth effect on all the genital tissues, including the cervix, vagina, vulva and breasts, disappears in two to six weeks after birth. Slight vaginal bleeding may follow a few days after birth, because of the drop in estrogen level. The endometrium then remains very thin and undeveloped until puberty occurs. This begins as a gradual awakening of the ovaries to produce a slowly increasing amount of estrogen, so that the endometrium becomes slightly thicker at the age of ten or twelve years, though it does not reach its full estrogenic effect until menstruation begins at the average age of thirteen years and eight months.

Precocious sexual development and early menstruation occur occasionally at the age of one, two, five, eight or ten years of age. Most often this is simply an early physiologic stimulation from the pituitary gland. Such a child may ovulate early, and an authentic case, Lina Medina of Peru, in 1939, gave birth to a 3900 gm. baby by Caesarean section, when she was only five years and eight months old. Her first menstrual period had appeared at the age of eight months. Because estrogenic hormone causes the epiphyses to close, these children usually are small of stature. If any child has not reached her height and begins to menstruate early, little further growth may be expected because of this closure of epiphyses. Various climates and states of health and nutrition affect the age of puberty. Poor health and faulty nutrition may delay the onset of menstruation to the age of sixteen or eighteen years.

A pineal tumor may produce macrogenitosomia precox in young males and much less frequently may produce precocious menstruation in girls. Fibrous dysplasia of bone, or "Albright's disease," is characterized by cystic bone lesions, brownish pigmented areas of the skin and sexual precocity limited to females. A more common cause of precocious bleeding and sexual development is the granulosal cell tumor, which may arise in the ovary at any age, with dramatic estrogenic effects in the prepubertal child and postmenopausal woman. The bleeding may be cyclic or irregular. The endometrium forms a typical hyperplasia pattern, and blood loss may be excessive. Diagnosis is suggested by the finding of a palpable adnexal mass, and may be confirmed by exploratory laparotomy.

With the onset of menstruation, the endometrium becomes moderately thick, with tubular, slightly curved glands, lined with tall columnar, non-secretory cells, with rather densely packed millet-seed like stromal cells (and both types of cells show occasional mitoses, indicating rather rapid growth of the endometrium), and with a surface epithelium of a single layer of tall columnar cells.

In the ovaries, which have been very slowly enlarging, several small graafian follicle cysts have been forming over a few years, the epithelium of which has produced estradiol. With the first menstruation, the estrogen level has come up to a peak, then has dropped precipitiously to a low level. The dominant follicle has receded and atrophied by a process known as atresia.

In the estrogenic endometrium of this first menstruation, the growth effect is obvious, but there is none of the secretory glycogen globules, no corkscrew tortuosity and feathering of glands, nor the swelling of the large pale superficial stromal cells, which may look like decidua sometimes, all caused, when present, by progesterone. As the unopposed estrogen drops from its high level, small ulcerations appear on the surface of the endometrium, and bleeding proceeds from the open arterioles. Sometimes very little of the endometrium may be shed throughout a period of anovulatory menstruation.

On the third, fourth, or fifth day of bleeding, the anterior lobe of the pituitary gland begins to secrete follicle stimulating hormone (FSH) again, and a small follicle, usually in the opposite ovary, chosen to be the dominant follicle of the coming cycle, begins to grow and to secrete estradiol. Several small follicles develop to less extent, to aid the estrogen production. The estradiol circulates through the blood stream; a part is metabolized by the liver to form estrone and estriol, and all three have their growth effect on all genital tissues, particularly the endometrium. The increasing level of estrogen has a hemostatic effect in the endometrium (and some think estrogen has a generalized hemostatic effect), the arterioles seal over, the ulcerations quickly heal by growth of the stromal cells and gland epithelium, and particularly by the growth of the surface epithelium. The endometrium, when entirely denuded, may heal with an intact surface in one or two days.

The stimulus from the pituitary gland and the subsequent secretion from the ovary may proceed in regular cylic repetitive action, so that bleeding occurs each month, but very often the stimulation lags and the build-up may occur over two, three or more months, and this is not unusual in the first years of menstrual function. While, occasionally, the young girl at puberty may ovulate regularly, beginning with the first menstruation, usually there is no ovulation, and only estrogenic non-secretory patterns of endometrium occur for approximately two years. During this time there is no pain. Dysmenorrhea occurs only if ovulation has preceded the menses. With unusually severe or complete cervical obstruction, pain occurs without ovulation. But even the very small cervical canal usually produces no obstructive pain.

At about the age of sixteen, sometimes much earlier, with others later, ovulation appears. The hypothalamus apparently controls secretory effects of the pituitary gland. In the first part of the cycle FSH (follicle stimulating hormone) alone is secreted to stimulate the granulosal cells of the dominant follicle. On the twelfth to fourteenth day from the first day of the last menses the pituitary gland suddenly secretes LH (luteinizing hormone), which apparently causes the graafian follicle to rupture and extrude the egg. With this rupture of the follicle, blood rushes into its center, and there is formed the young corpus luteum hematoma. This trauma staggers the ruptured follicle so that for one to three

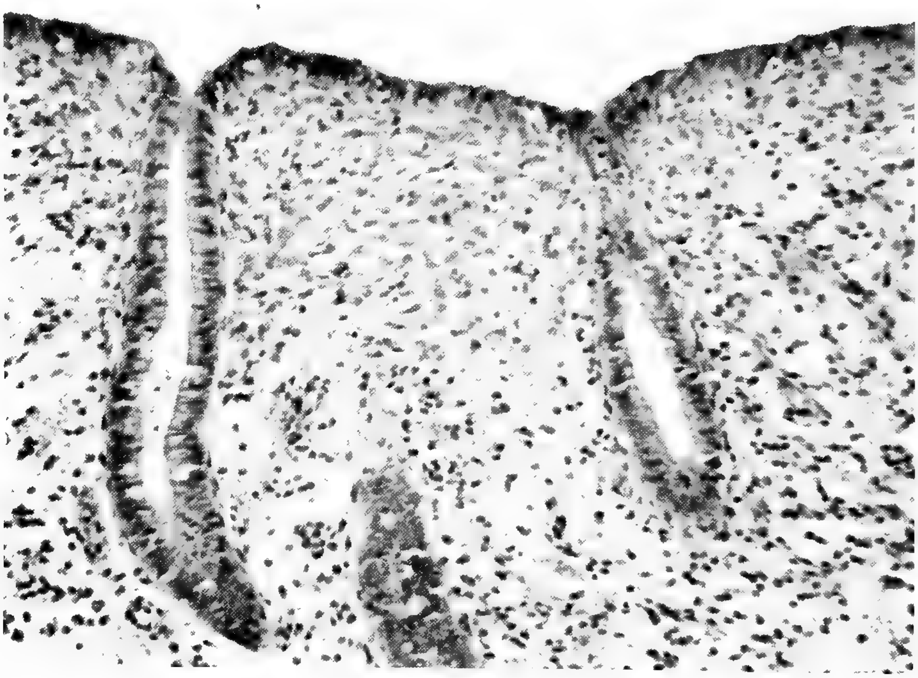


Fig. 119. Post-menstrual endometrium. About four or five days after cessation of the menses. The glands are straight, show no glycogen globules, and the stroma is loose. Some of the clear areas in the epithelial layer represent migrating cells or secretion other than glycogen.

days the estradiol secretion decreases, then the follicle recovers and the estrogen continues its upward climb. The pituitary gland secretes FSH and LH in continuous and increasing amounts, and a new hormone, the luteotrophic hormone (LTH) begins to stimulate the newly formed corpus luteum to secrete progesterone, in addition to estradiol. Both the pituitary and ovarian hormonal levels increase up to two days before menstruation. Then the hypothalamus abruptly ceases to stimulate the pituitary gland, the FSH, LH, and LTH quickly recede, and as a result the corpus luteum ceases its production of estrogen and progesterone, so that the levels of both drop quickly. Two days or so after this removal of hormones, menstruation ensues.

The endometrium lining the uterus at the end of menstruation consists of a thin layer of basalis, containing small non-secretory glands, surrounded by a dense stroma, with a ragged uncovered surface. The estrogen must be at a very low level at this instant, although probably some estrogenic hormone from the ovaries or adrenals undoubtedly is present. With the stimulus of the FSH on the new dominant graafian follicle, within twenty-four hours the endometrium may have a restored and intact surface epithelium, which grows out from the epithelium of the glands. The endometrium begins to thicken, the glands become elongated, very straight with the rapid growth and have non-secretory epithelium in their lining. The period of five or six days from the end of menstruation through regeneration and the growth of straight endometrial glands is known as the "postmenstrual phase."

From the estrogenic effect the endometrium becomes steadily thicker, and the glands take on mild, sweeping curves, and remain non-secretory. This phase over five or six days is known as the "early interval phase." The postmenstrual and early interval phases are grouped together by many as the "proliferative phase."

When the LH stimulates the ovary to ovulation and the small bluish granulosal cells in the collapsed follicle become large, fat-containing, and finely granular, which process is known as luteinization of the granulosal cells, not only estradiol but also progesterone are secreted into the blood stream. After a lag of two or three days from ovulation, the progesterone begins to show its earliest effect in the formation of globules of glycogen beneath the nuclei of the cells lining the endometrial glands. The glands gradually de-

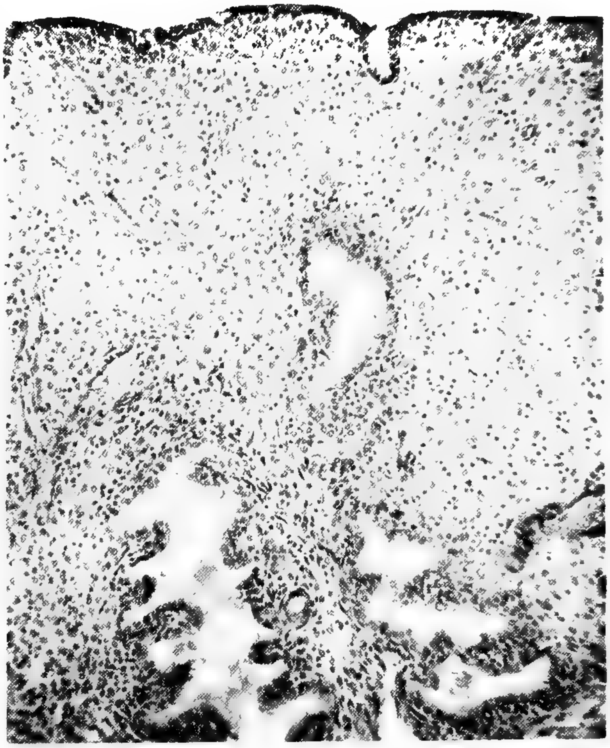


Fig. 120. Premenstrual endometrium with decidual type change. This is a markedly progestational effect involving particularly the stromal cells in the zona compacta in which they are much enlarged, pale staining and contain much glycogen. The deeper glands in the zona spongiosum are of the typical corkscrew type, have ragged cells, which have discharged their glycogen into the lumen of the gland. They tend to be exhausted of their glycogen. This endometrium may be normal, occurring immediately before a menstruation, although one would think that there is excess progesterone present. It also may be present in the earliest stage of pregnancy.

velop a very full curve, and the globules of glycogen, which appear as clear vacuoles in the cells with hematoxylin and eosin stains (a brilliant red with Best's carmine stain), pass around the nuclei of the cells lining the glands to appear near the lumen of the glands. This is known as the "late interval phase," comprising some six to eight days.

In the last five or six days before menstruation, there occurs the "premenstrual phase"; the glands become corkscrew-like, with feathering, and the lining cells burst open, discharging the glycogen into the lumen of the glands, so that the cells appear very ragged. While some globules of glycogen may remain in the cells, many of the cells appear flattened and exhausted, while the lumen of the glands contain abundant glycogen. The single layer of surface cells reacts as those lining the glands. The stromal cells become very loosely arranged, and more pale staining. Commonly the stroma in the superficial endometrium (the zona compacta) may show varying degrees of swelling of the cells, due to formation of glycogen within them, so that a decidua-like change may occur normally. Rarely, such a change may be indistinguishable from true decidua, which by definition connotes associated pregnancy. Small spiral arterioles extend up from the zona basalis, through the loose zona spongiosa with the prominent corkscrew glands, into the zona compacta, where the glands are compressed into duct-like formations due to pressure from the swollen superficial stromal cells. These spiral arterioles, which are rather thick-walled and readily seen in the ordinary stained slides, become sensitized to progesterone, which acts as a dilating agent. When the progesterone supply ceases, due to the abrupt cessation of function of the corpus luteum, the progesterone in the blood disappears in about forty-eight hours. This is followed by localized spasm of the spiral arterioles for a period of several hours (as shown by Markee in endometrial transplants in the anterior chamber of the eye of the monkey). The spasm stops the blood circulation in the distal end of the arteriole, oxygen is deprived from the stroma and distal glands, and localized necrosis follows. The arteriolar spasm relaxes and blood rushes into the distal area, now necrotic. This process takes place in many minute areas in the zona compacta. Small defects are cast off in the blood trickling into the endometrial cavity. Gradually the necrosis spreads, allowing the superficial endometrium to come away as necrotic cells or by dislodging separate fragments of the endometrium. On each succeeding day of menstruation the shedding of endometrium extends deeper, presumably with recurrent arteriolar spasm at lower levels. By the end of menstruation on the fifth, sixth or seventh day, the endometrium has been cast off down to the basalis. New estrogen from the ovaries apparently causes the vessels then to seal over, bleeding ceases and healing occurs rapidly by the extension of a single layer of columnar epithelium from the open basilar glands.

The length of the menstrual cycle varies normally from twenty-one to thirty-five days, and averages around twenty-eight days. But women rarely, if ever, menstruate regularly to the day, so that each month the variation is at least one, two or three days. It is surprising to the male that women are indefinite regarding the time of an event so remarkable as bleeding, but normal function in an individual becomes common-place and makes little impression.

The time of ovulation has been studied by various methods, including the accumulation of data from observation of the ovaries at operation, a comparison of histology of the endometrium and ovaries, the recovery of ova from the fallopian tube, the timing of Mittelschmerz, timing of differences of electrical potential at ovulation, the Knaus uterine reaction to pituitary extract, investigating the age of embryos, determining the age of the corpus luteum, controlled mating with single intercourse or donor insemination, basal temperature shift and vaginal smear changes. It appears that a most constant finding is the occurrence of ovulation fourteen days before the ensuing menstruation (Knaus). The corpus luteum always lives fourteen days, unless it is defective, in which case menstruation may be precipitated early, or irregular scant bleeding may begin and continue up to the menstrual period. Or the corpus luteum may be prolonged pathologically in partial function, to produce a prolonged menstruation (menorrhagia, here known as irregular shedding of the endometrium), or a corpus luteum cyst may cause a delayed menstruation.

The amount of blood loss during menstruation varies from thirty to 500 cc., probably averaging ninety to one-hundred and twenty cc.

CHANGES ASSOCIATED WITH THE MENSTRUAL CYCLE

There are undoubtedly many systemic and rhythmic changes in the body associated with the menstrual cycle that are not recognized, and it will not be surprising if in the future some other simple and obvious rhythmic functions are pointed out. At this time only a few facts are known. The basal body temperature, the temperature of the body after complete rest and without the stimulation from any exercise, ingestion of food or emotional excitement, has a characteristic cycle, which is clinically useful. The basal temperature, called the "waking temperature" by the British, should be taken on awakening by mouth, by vagina, or by rectum. The oral method may be inaccurate because of breathing, talking, and friction of the tongue. In the vaginal method, thermometers have been broken, or surprisingly but truly, have slipped into the bladder. The rectal method may be less aesthetic and more inconvenient, yet it is undoubtedly the most accurate method available. Because of the diurnal variation, the temperature should be taken at the same time daily.

The rectal temperature of the normal male, or postmenopausal woman, is about 98.6 degrees when taken under basal conditions. If estrogen is given to either, the temperature approximates 97.6 degrees. In the woman, during menstrual life immediately after menstruation the rectal temperature hovers around 97.6 degrees, her normal temperature having been lowered one degree by her own estrogen. Very soon after ovulation, as progesterone is manufactured by the lutein cells and is secreted into the blood stream, the temperature-depressing effect of the estrogen is neutralized by the progesterone, and the basal temperature rises one degree to normal, even though estrogens continue in increasing amounts. The temperature remains around 98.6 degrees until one or two days before menstruation when it drops sharply again, due to removal of the progesterone and the unopposed temperature-depressing effect of the estrogens. This temperature shift is useful in determining that progesterone was present and presumably that ovulation occurred during this cycle. When the temperature remains flat, at around 97.6 degrees, only a follicle, and no corpus luteum is assumed to have developed.

Premenstrual tension is another normal cyclic change. After ovulation has occurred and progesterone has been added to the endocrine effects, a woman develops a normally increased nervous tension, which progresses up to the time of menstruation. This may be greatly exaggerated if the patient has anxieties, pressures, tensions and problems of life, which cause unhappiness. In the same progestational period, the sodium ion increases in the tissue spaces, so that at times water retention is marked. This may amount to six or eight pounds in one cycle, though that much is unusual. Diuresis and weight loss follow after menstruation starts. The association of abnormal premenstrual tension with degrees of water retention has suggested that displacement of the sodium ion and prevention of edema may relieve the nervous symptoms. In order to remove some of this sodium ion and associated edema, table salt (sodium chloride) is removed from the diet, and one gram of ammonium chloride or potassium nitrate three times daily (the latter may cause less gastric discomfort) may be prescribed in the last two weeks of the cycle. Recently the newer diuretics (as diuril) have seemed quite helpful. If the premenstrual tension, when symptomatic, is caused by anxiety, it seems unlikely that the sodium ion is involved. Progesterone has been given in the last half of the cycle in increasing amounts with many reports of improvement (including a report by this author), but the good results probably were psychological. Progesterone in the normal corpus luteum seems to induce the normal tension, as prevention of ovulation or removal of the ovaries stops this cyclic change. In some instances where hysterectomy is necessary near the menopause and there is associated severe premenstrual tension, simultaneous removal of the ovaries may have a relaxing effect, especially after a small maintenance dose of estrogen. Of course the operation does not cure the family problems so often involved, but life may seem on a more even keel. Ordinarily, best results follow correction of emotional conflicts, but sympathy and encouragement, interspersed with mild sedatives (as phenobarbital gr. 1/4 three times daily, or the tranquillizing drugs) are most helpful.

Another cyclic change that usually is obvious occurs in the breasts. To a certain extent the size of the breasts is related to the amount of estrogen present. In individuals with ovarian dysgenesis and absent estrogens, the administration of estrogens of natural or synthetic origin may produce marked growth effect on the breasts, which may become well developed and firm. On the other hand, the individual with normal ovaries and small breasts will show little or no change after estrogen therapy. Obviously there are other factors in breast growth and development than estrogen and progesterone.

However, each month the increasing estrogen causes proliferation and extension of the ducts out to the acini. Progesterone, when it appears, causes enlargement of the acini, particularly in the individual cells. These hormonal changes through the breasts cause a diffuse enlargement with frequent pain and tenderness. Areas of lumpiness commonly occur throughout the breasts, becoming most marked before menstruation. Such lumps have been spoken of as chronic cystic mastitis, and while small or even large cysts commonly are associated, inflammation is absent. A fibrosis seems to form around the acini which may become permanent, but more often the thickening comes and goes, and the symptoms become worse and better. Since these masses, and the pain and tenderness, occur mainly in the premenstrual period, it would seem that progesterone must be a factor in their formation. This condition has been treated with both progesterone and estrogen, parenterally and orally, with equivocal and probably no beneficial results. Testosterone seems to have some temporary but no lasting benefit. Reassurance and proper breast support have proven the best therapeutic agents. The only real difficulty with lumpy breasts, or so-called chronic mastitis, is the differentiation of coincidental carcinoma of the breast. Often biopsy is necessary to make certain, and constant observation is indicated.

Vicarious menstruation, bleeding from the nose, lungs, rectum, etc. at the time of menstruation, has never been associated with ectopic endometrium, except rarely in the umbilicus or bowel. Usually bleeding from these areas is really not cyclic, as reported, and must be related to capillary fragility which is increased with menstruation.

ANOVULATORY MENSTRUATION

The early menstrual periods in nearly all young women are anovulatory, that is, the egg is not extruded from the ovary and the endometrium remains non-secretory, continuing in the same early interval phase up to menstrual bleeding. The follicle stimulating hormone is secreted, but L. H. and L. T. H. never appear. The graafian follicle develops as for ovulation, but continues until two or three days before the onset of menstrual bleeding. When the F. S. H. is removed, the follicle ceases to produce estradiol and atrophies (atresia), the estrogen level drops in the blood, small ulcers appear on the endometrial surface and bleeding occurs. Apparently at times much of the endometrium is retained; certainly it does not become necrotized, fragmented and completely sloughed away as after the effect of progesterone. The reappearance of F. S. H. and estrogen from a new follicle causes cessation of bleeding and healing of the endometrium.

This type of endometrial cycle is the rule in girls of fourteen to sixteen years of age, though variable, and it is common in women who are near the menopause. After the fortieth year, anovulatory menstruation becomes more frequent, and particularly from forty-five to forty-seven years. At the average age of forty-seven years menstruation ceases.

Apparently anovulatory cycles may occur occasionally throughout menstrual life, but this is evidently quite uncommon. Even among women complaining of sterility, such a cycle is rare unless the patient has amenorrhea or metrorrhagia. Anovulation may occur once or twice a year in normal and regularly menstruating women, but this is sporadic and not a repeated occurrence. Information has been obtained indirectly by endometrial biopsy and, in recent years, more popularly and less painfully by records of the basal body temperature.

HYPOMENORRHEA AND OLIGOMENORRHEA

Hypomenorrhea or scant menstruation usually is of no pathological significance. Ovulation is present as a rule, fertility continues, and there is no effect on general health, though at times patients are much concerned.

Hypomenorrhea may be associated less often with anovulation and sterility. Subclinical hypothyroidism may be the cause, and if the patient has complaints of fatigue, dry skin, has a slow pulse and lowered blood pressure, then the basal metabolism test is indicated, and thyroid extract may be prescribed with frequent remarkable improvement. As a woman becomes older, the blood loss at the menses lessens, particularly shortly before complete cessation. But a scant flow does not always mean the menopause is imminent.

Oligomenorrhea, few or infrequent menses, is the term used when menstruation occurs at intervals of two, three or four months. The physical examination may be normal, and infrequent menses may be of no importance, not interfering with fertility. Probably the majority of cases with oligomenorrhea do ovulate, though always delayed, as every normal ovulation is followed fourteen days later by menstruation, if pregnancy has not occurred. Since only one ovulation precedes these infrequent menstruations, the chances of pregnancy are less frequent than in patients with regular menstruation. On the other hand, some patients with oligomenorrhea do not ovulate, and this is indicated most readily by the basal temperature graph, and also by endometrial biopsies, provided they are taken within ten days or less of the ensuing menstruation.

Patients with oligomenorrhea also may have a lowered thyroid activity, and if there is sterility or other symptoms, the basal metabolic rate should be obtained and thyroid extract should be prescribed if indicated. The production of ovulation and more regular menstruation has been reported after intravenous or intramuscular injections of equine gonadotropin, but this therapy is not popular at present because of equivocal results and, more importantly, because of possible serum reactions. The latter, while very infrequent, may be serious. Intravenous estrogen (Premarin) has been advocated recently to produce ovulation in oligomenorrhea. The possibility of the Stein-Leventhal syndrome should be considered. Until recently, irradiation therapy to the pituitary and ovary has been used to stimulate these glands to greater function, but suddenly fear of injury to the genes has interrupted this type of therapy.

PRIMARY AMENORRHEA

Primary amenorrhea denotes permanently absent ovarian function. The diagnosis may be difficult to differentiate from delayed menarche, as some young women menstruate for the first time at eighteen or twenty years of age. But, as a rule, with delayed menarche there is evidence of estrogens being present, which cause growth of the breasts, of pubic hair and of the vagina. The latter gradually arrives at its full thickness some months, or a year or two before the onset of menstruation. In delayed menarche, improvement in general health, maintenance of proper weight, administration of small doses of thyroid, and sometimes induced bleeding by estrogen or estrogen-progesterone withdrawal, may be followed by normal spontaneous menstruation. But in primary amenorrhea the girl usually is small for her age, an evidence of hypopituitary growth effect, and may have early closure of epiphyses. The secondary sex characteristics show little or no development, as evidenced by flat breasts, absence of pubic hair, the thin vagina, a minute uterus and non-palpable ovaries. As a rule, the gonads are so small as to be almost indistinguishable at exploration; so that while not completely absent, this condition has been called "ovarian agenesis," and now more properly "gonadal dysgenesis."

Further studies of these individuals show in some, if not all, a male sex chromatin pattern in the nuclei of cells from various parts of the body (the skin, vaginal and nasal smears, and polymorphonuclear leukocytes have been used). This seems to indicate these individuals are genetic males. But psychological studies have shown them to have predominate female reactions. Since there is no possibility of stimulating these rudimentary and imperfectly formed sex cell masses, which represent embryonic gonads, treatment is by substitutional hormone therapy. The continuous administration of small doses of oral estrogens produces a remarkable development of breasts, subcutaneous fat, pubic and axillary hair, and growth of the vagina and its epithelium. Periodic bleeding which seems very beneficial psychologically, can be induced by giving stilbestrol five mgm. daily for twenty of each twenty-eight days, or by giving stilbestrol one mgm. or conjugated estrogens (Premarin) one and twenty-five hundredths mgm. daily for twenty days, then administering one or two injections of progesterone or one injection of estrone and aqueous progesterone (Cyclogestrin). Withdrawal bleeding follows in three to six days. On the twenty-eighth day the oral estrogen is repeated for twenty days. This medication is continued indefinitely, and the patient is examined at intervals of several months.

With substitution therapy and induced menstruation patients with primary amenorrhea improve tremendously. Height does not increase, but the girls become quite feminine in appearance, are much attracted by and to the male, marry and are happy in their sex relations. They are apprised early of their sterility, but encouraged to be normal women otherwise. That they may be genetic males does not interfere with the fact they are psychologically and somatically females.

SECONDARY AMENORRHEA

Cessation of menstruation after a normal onset indicates either pregnancy, the menopause, or secondary amenorrhea. If the vagina has become thin and the rugae have atrophied, and if the washings or smears show round or oval epithelial cells (parabasal cells) from the vagina, then there is absence of estrogen, the ovaries apparently have ceased their function, and the patient is in the menopause, which is irreversible. If the vagina is thick, with essentially normal rugae, and the cells are large, hexagonal and contain small nuclei, the ovaries may be assumed to be secreting estrogen and to be in a resting non-cyclic phase. As a rule menstruation either will start spontaneously or may be expected to follow treatment.

The causes of secondary amenorrhea are (1) systemic chronic illness, such as tuberculosis, diabetes, etc., (2) obesity, (3) subclinical hypothroidism, and (4) psychogenic factors. Each patient should have a reasonably careful general physical examination and appropriate laboratory examination to rule out organic disease. Obesity is a common cause of menstrual irregularities, particularly secondary amenorrhea. Usually there is a history of rather rapid increase in weight at the time the menstrual abnormalities begin. Just how the increased amount of fat causes amenorrhea is not clear; perhaps some disturbance in the hypothalamus produces increased appetite, as the hypothalamus ceases to stimulate the pituitary gland. Emotional disturbance often is associated with obesity, and emotions may affect the hypothalamus. Subclinical hypothyroidism (in contrast to frank myxoedema) is a frequent diagnosis by the gynecologist. Women with lowered thyroid activity, when treated with thyroid extract, may show remarkable improvement. The psychogenic factor as a cause of amenorrhea is being discussed with increasing frequency. It is readily understood that a normally menstruating mother may develop amenorrhea from a severe emotional shock, such as might occur from the sight of her child being run down by a truck and killed. But it is difficult to understand how an attractive young woman, with no more than the usual nervousness and no more than the usual problems of life, should have amenorrhea of psychogenic origin, when others in almost similar or more difficult situations have regular menstruation. If the psyche is the most important cause of secondary amenorrhea (and many insist this is true), then the clinician and gynecologist must learn much from the psychiatrist.

The treatment of secondary amenorrhea (and pregnancy must be excluded) includes treatment of any systemic disease, hypothyroidism, obesity and psychogenic difficulties. A cooperative, obese patient who will reduce weight, and the hypothyroid patient who is given the proper amount of thyroid extract, may have pleasant and simple solutions of their problem. Because experimental evidence indicates that very small doses of estrogen may stimulate the pituitary gland, this medication has been used for secondary amenorrhea (stilbestrol one-tenth mgm., Premarin three-tenths mgm. etc.,), but with indefinite results. Some patients have seemed improved. Irradiation stimulation of the pituitary gland and ovaries caused extraordinarily improvements in many patients with secondary amenorrhea, but because of mutations and congenital abnormalities caused by minute amount of irradiation in experimental animals (the fruit fly, mouse), a strong trend against this method of treatment has developed recently.

The Stein-Leventhal syndrome also is more frequently diagnosed, sometimes too frequently. Many years ago follicular cysts were resected from the ovaries, whether the patient had normal menstruation, metrorrhagia, or amenorrhea. It became apparent twenty-five or thirty years ago that this surgery was of no value, as the follicular cyst was produced by stimulation from the pituitary gland and could be expected to recur if the stimulus continued, or to recede without attacking the ovary if the excess stimulation abated. When Stein and Leventhal proposed wedge resection of ovaries for amenorrhea in 1936, evidently many felt this was part of the same useless surgery, but these authors insisted they were speaking of a particular kind of case, one with mild to moderate hirsutism, secondary amenorrhea or oligomenorrhea, and polycystic ovaries. The ovaries are diffusely enlarged with thickened capsules and with multiple *minute* follicular cysts throughout the cortex. The picture was confused somewhat by the insistency that the diagnosis should be substantiated by gynecography, oxygen being injected into the abdomen through a needle (later carbon dioxide was injected by the Rubin's cannula through the uterus and fallopian tubes). Enlarged ovarian shadows were demonstrated by the x-ray film, the hips being elevated to displace the gas into the pelvis for best outline of the ovaries. Just how longitudinal wedge resection should aid these patients to cause regular menstruation and desired pregnancy is a mystery, but with increasing frequency small series are being reported with a high percentage of good results. Perhaps the hypnotic effects of the gynecologists on the psychogenic causes are enhanced by the intricacies of the diagnosis and operation. It does appear that these large, thick-surfaced ovaries, with the multiple minute cysts, are different from the orginary follicular cystic ovaries, associated with normal menstruation or metrorrhagia. Much is to be learned of the endocrine relationship in this situation.

Of late, some patients with secondary amenorrhea have been found to have slightly elevated urinary excretion levels of 17-ketosteroids (from fifteen to twenty-five mgm. per twenty-four hours), the normal being from four to twelve mgm. Usually slight hirsutism has been associated with this condition. Early androgenic tumors of the ovary and adrenal gland must be considered, but these are ruled out if a trial of treatment with cortisone or its newer chemical descendants should cause decrease of the 17-ketosteroids and subsequent menstruation. This syndrome must indicate mild adrenocortical hyperplasia, and these uncommon cases may include the Stein-Leventhal syndrome.

Cyclic bleeding may be induced by estrogen alone, e. g., stilbestrol five mgm. daily for twenty days, after which withdrawal bleeding occurs three or four days later, caused by the falling estrogen level. Most cases with secondary amenorrhea have sufficient estrogens present, so that progesterone alone given over a short period of time, (as fifty mgm. in oil intramuscularly for two doses on alternate days), is also followed by withdrawal bleeding from the fragmentation necrosis of the endometrium, characteristic of the withdrawal of progesterone. A fair amount of estrogen must be present, if withdrawal bleeding is to follow administration of progesterone. Some patients have insufficient estrogen from their own ovaries and must be given estrogen for priming, either simultaneously with the progesterone (e. g., cyclogestrin, aqueous, a combination of estrone and aqueous progesterone), or as an oral tablet of stilbestrol, premarin, etc., for one or two weeks.

This artificial bleeding is of psychological benefit. After three or four induced cycles, regular menstruation may follow. On the other hand, not infrequently this therapy is disappointing, and spontaneous menstruation does not follow.

METRORRHAGIA

Prolonged and irregular bleeding from the uterus is an objective symptom of the patient, and the term metrorrhagia commonly is used as a diagnosis by the physician, although it certainly does not clarify the cause. This type of bleeding occurs particularly after puberty and immediately before the menopause. Although more frequent at puberty and near the menopause, prolonged and irregular bleeding may occur in every year of menstrual life. The cause of the bleeding may be related to organic disease, such as myomas of the uterus, pelvic inflammatory disease, pregnancy disorders and incomplete abortion, and malignant growths. Rarely a blood dyscrasia may be a cause, such as thrombocytopenic purpura, splenic anemia, etc. After the exclusion of these conditions, which require complete examination, careful pelvic palpation, and most importantly, curettage of the uterus, the diagnosis may be clarified as functional uterine bleeding, or metrorrhagia. The diagnostic curettage must be stressed because of the possibility of malignancy in every patient; this procedure must never be delayed. Some have said that any abnormal bleeding means carcinoma until proved otherwise. Certainly every patient with abnormal bleeding should have careful physical examination. If the cervix and uterus look and feel normal and there is no ovarian tumor, *abnormal bleeding during any one cycle is observed.* But *if the*

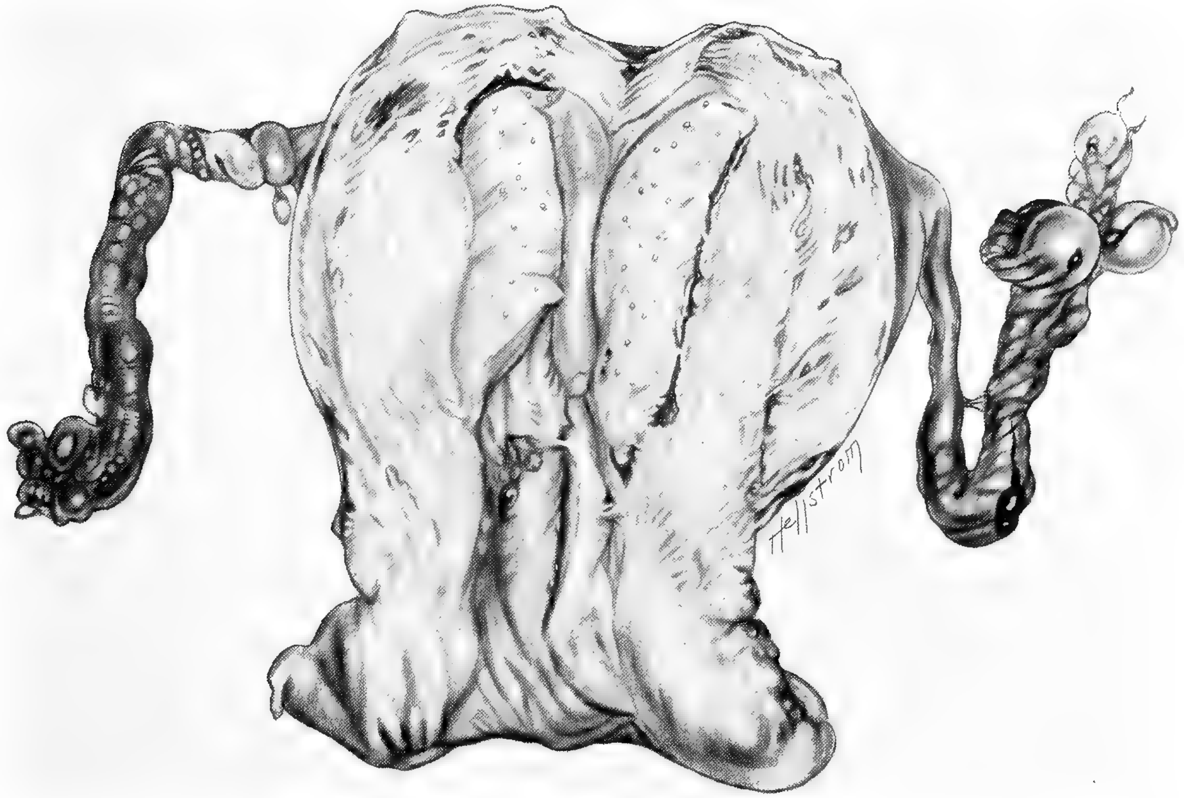


Fig. 121. Endometrial hyperplasia. The endometrium is quite thick and the small cystic spaces are visable in this unusual specimen. More often the endometrium is quite polypoid when the hyperplasia is of this degree. The tubes show mild chronic salpingitis and there are multiple small hydatids of Morgagni.

bleeding recurs in the next cycle as intermenstrual or prolonged irregular bleeding, *diagnostic curettage is indicated.* This is primarily to rule out malignancy, but curettage also removes polyps and has a curative effect, stopping the bleeding and being followed by a reversion to a normal cycle in a generous proportion of cases.

With metrorrhagia, or functional uterine bleeding, or prolonged irregular uterine bleeding, the endometrium shows either interval non-secretory endometrium, or its more advanced estrogenic state, endometrial hyperplasia, in eighty percent or more of all cases. The pituitary gland is then secreting F. S. H., but no L. H. or L. T. H. The graafian follicles in the ovary are stimulated to grow and form multiple small follicular cysts. In contrast to the micro-follicular cysts, which are three to four mm. in diameter, these vary from five mm. to two cm. in diameter. The follicles secrete only estrogen in varying amounts, and no progesterone. The estrogen stimulates the endometrium to grow to the early interval non-secretory stage. When the estrogen level remains constant or continues to rise, no bleeding occurs, and sometimes one, two or three menses may be skipped; but more often the estrogen level presumably fluctuates, which causes irregular bleeding. It has long been known that a drop in a sustained estrogen level causes bleeding from small ulcers on the surface of the endometrium. Such bleeding may be continued over a week or two or three, or there may be continuous bleeding over several months, presumably because of fluctuations of the estrogen level. The exact mechanism here is not clear.

Frequently the estrogen level tends to rise above the normal (to reach high peaks or to have sustained relatively high levels), causing the endometrium to become thicker than average, sometimes quite overgrown and polypoid (one or two centimeters thick), and to show a marked growth effect in the glands and stroma. The latter is indicated by the full-bodied appearance of the bluish elongated stromal cells with frequent mitoses in their nuclei, indicating rapid growth, and by piling up two or three layers of tall bluish non-secretory cells lining the glands. Apparently because of the overgrowth and multiplication of these lining cells, the glands tend to dilate to form cyst-like spaces in the upper or midportion of the glands. The dilatations in the microscopic sections show cystic spaces of varying size, suggestive of holes in Swiss cheese. Cullen gave the name *"endometrial hyperplasia"* and "swiss-cheese endometrium" over fifty years ago.

If the endometrium of patients with endometrial hyperplasia is biopsied at intervals of two weeks over a period of time, the pattern is seen to change from endometrial hyperplasia to interval non-secretory endometrium and back again. Sometimes the interval non-secretory appearance has a marked piling up of epithelial cells, but more often the endometrium cannot be distinguished from that of the twelfth or thirteenth day of the normal cycle. It does appear that if curettage reveals one or the other type, both may be part and parcel of the same anovulatory dysfunction with excess or prolonged estrogen stimulation.

The cause of marked or severe metrorrhagia is less clear than that of amenorrhea. Organic pelvic diseases, such as tumors, inflammation and disorders of pregnancy, are to be carefully separated. Systemic disease is rarely a factor, but is not to be completely dismissed. Obesity occasionally is of little causal importance, and should be treated if present. Hypothyroidism may be a definite factor, but often is not related. The psychogenic factor, at times of great importance, is again to be considered. The occasional patient with marked nervous tension and abnormal bleeding may show great improvement after simple sedatives, and cure when her problems are not too perplexing. This situation often applies with minor metrorrhagia, intermenstrual bleeding, and particularly menorrhagia. The well marked endometrial hyperplasia of some

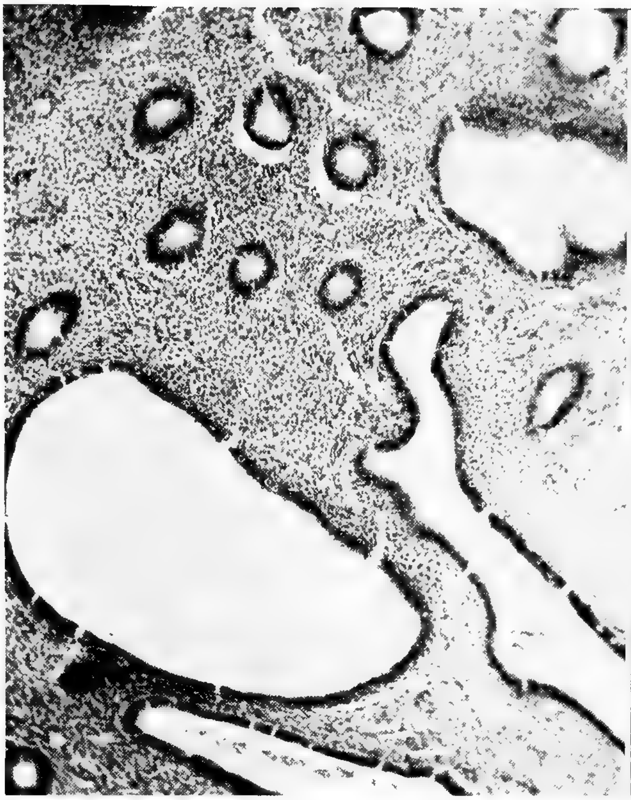


Fig. 122. Endometrial hyperplasia. The typical "swiss-cheese" endometrium. The glands have non-secretory epithelial cells, often piled up two or three cells thick, have a slight or moderate curve and many are dilated to form cystic spaces. This is the typical effect of prolonged unopposed estrogen or hyper-estrogenic effects in the endometrium.

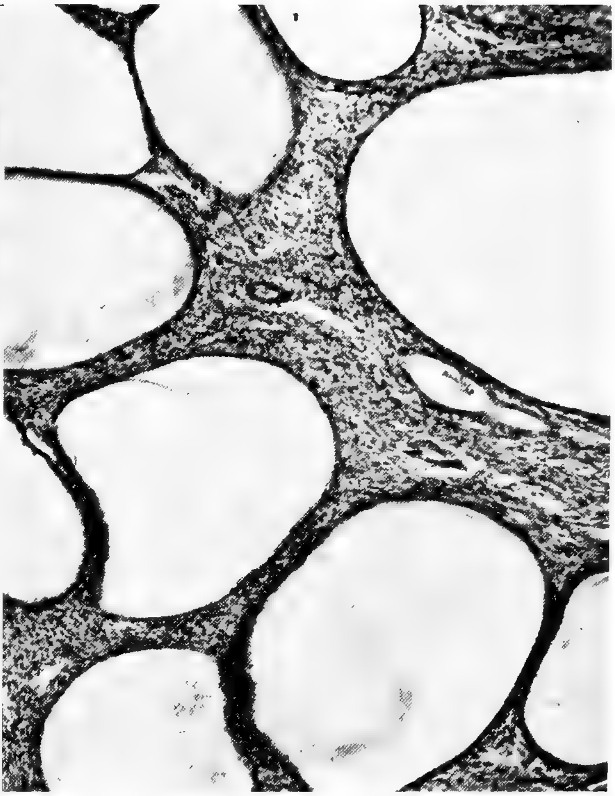


Fig. 123. Postmenopausal endometrial hyperplasia. The endometrium may be thicker than normal, or perhaps thinner than normal. The glands are markedly dilated and lined by very low or flattened epithelial cells. The stromal cells are atrophic. This is inactive endometrium, and the cause of the cystic changes is unknown.

standing seems not to have much of a psychogenic origin. Little or nothing is known of the cause of this disease. The follicular cysts secrete too much estrogen, and the pituitary secretes too much F. S. H. and no L. H. and L. T. H. But why?

The treatment of metrorrhagia is somewhat more satisfactory than an explanation of its cause. The first step is curettage of the uterus. This is necessary as a means of ruling out malignancy, as a method of studying the endometrium and hormone effects, and as an important form of therapy. After a single thorough curettage, fifty per cent of all patients will revert to normal cycles. The percentage of cure depends on how major the metrorrhagia is and how well-marked the endometrial hyperplasia may be, as the more minor disturbances are more readily cured. Cure of secondary anemia, correction of obesity or malnutrition, administration of thyroid extract as indicated, and mild sedation in some cases, are factors that may aid reversion to normal cycles.

The use of progesterone to produce regular controlled bleeding for several months is valuable in the severe bleeding cases. This has been known as the "medical curettage" of Albright. Progesterone, when given intramuscularly, by mouth, or in vaginal suppositories, may be used to sensitize the arterioles of the endometrium, so that when all the progesterone is metabolized and excreted, its withdrawal apparently will cause spasm of the spiral arterioles, with subsequent necrosis, bleeding and shedding of the endometrium. The intramuscular use is the least variable in its effect, and is best given as fifty mgm. in sesame oil in two doses with one day interval, repeated each twenty-eight and thirty days for four months. Three days following the second injection, bleeding and desquamation occur. The first withdrawal bleeding after progesterone may be so profuse as to require bed rest, ice-bag, sedation, testosterone propionate (fifty mgm.) intramuscularly, and rarely blood transfusion, but subsequent withdrawal bleedings are like normal menstruation. This progesterone withdrawal bleeding or "induced menstruation" may be continued for months or years without harm. A combined injection has been used, containing a large dose of estrogen to stop the bleeding already under way, by rapidly increasing the estrogen level (though already high), progesterone to sensitize the spiral arterioles and to effect the shedding of the endometrium when the hormone is metabolized, and testosterone propionate to reduce the profuseness of the withdrawal bleeding (though bleeding is never excessive after the first cycle). Ordinarily, progesterone alone is quite satisfactory.

The medical curettage, or progesterone-induced menstruation, is particularly useful in the treatment of metrorrhagia in young girls with so-called pubertal bleeding. In these instances, the improbability of malignancy obviates operative diagnostic procedures. Pelvic examination, or at least careful rectal and abdominal palpation, should be performed. Carcinoma of the cervix and granulosal cell carcinoma of the ovary have produced hemorrhage in young girls, but both are rare, the former especially so. But in women after the age of twenty-five years, surgical curettage and microscopic study of the endometrium always should be performed before endocrine therapy is prescribed.

Estrogenic therapy also has been used widely for control of irregular bleeding. The administration of estrogen orally for twenty days, then omission of the drug for eight days, causes no bleeding while the estrogenic level is ascending, but is followed by withdrawal bleeding when the estrogenic level rapidly declines. Estrogenic therapy may be given as stilbestrol one, three or five mgm. daily for twenty days (better results occur with the larger dose, but twenty per cent of patients have nausea from the stilbestrol), as Premarin 3.75 or 5 mgm. daily (better results occur with the larger doses), or other estrogens. Estrogenic therapy does not cause the endometrium to shed as thoroughly as does progesterone, and a generous amount of endometrium may be retained from month to month.

Thyroid extract seems of value in some cases, and is always to be considered. Proper body weight should be achieved. Anemia should be corrected. Emotional tensions must be cushioned by sympathetic understanding, good advice, and mild sedation, as indicated.

Resection of follicular cysts of the ovaries, usually present with metrorrhagia, has been abandoned because of poor results.

Cases of minor metrorrhagia (with a short history especially) are cured easily as a rule or commonly cure themselves. But major metrorrhagia, prolonged bleeding over months or years, with well formed endometrial hyperplasia may seem impossible to cure. In the past, very young girls occasionally had irradiation therapy or hysterectomy. It seems now that cyclic progesterone therapy should control most or all cases. Marked metrorrhagia near the menopause, which does not respond to one or two curettages, usually is best treated by hysterectomy. In these cases associated lesions, as enlargements of the uterus, small myomas, chronic cervicitis, polyps, adenomyosis, and degrees of prolapse are often additional reasons for hysterectomy.

The best hormone therapy comprises the use of progesterone, given in the proper and regular manner. Usually it is given temporarily over four cycles, always in the hope that nature will take over with spontaneous ovulatory cycles (some believe progesterone aids ovulation, but this is doubtful). Often there is recurrence of metrorrhagia, and more cyclic therapy with progesterone may be required. Occasionally the progesterone may be necessary almost regularly for several years, before nature may take over and eventually produce ovulation, and even reward those who persevere with normal pregnancies.

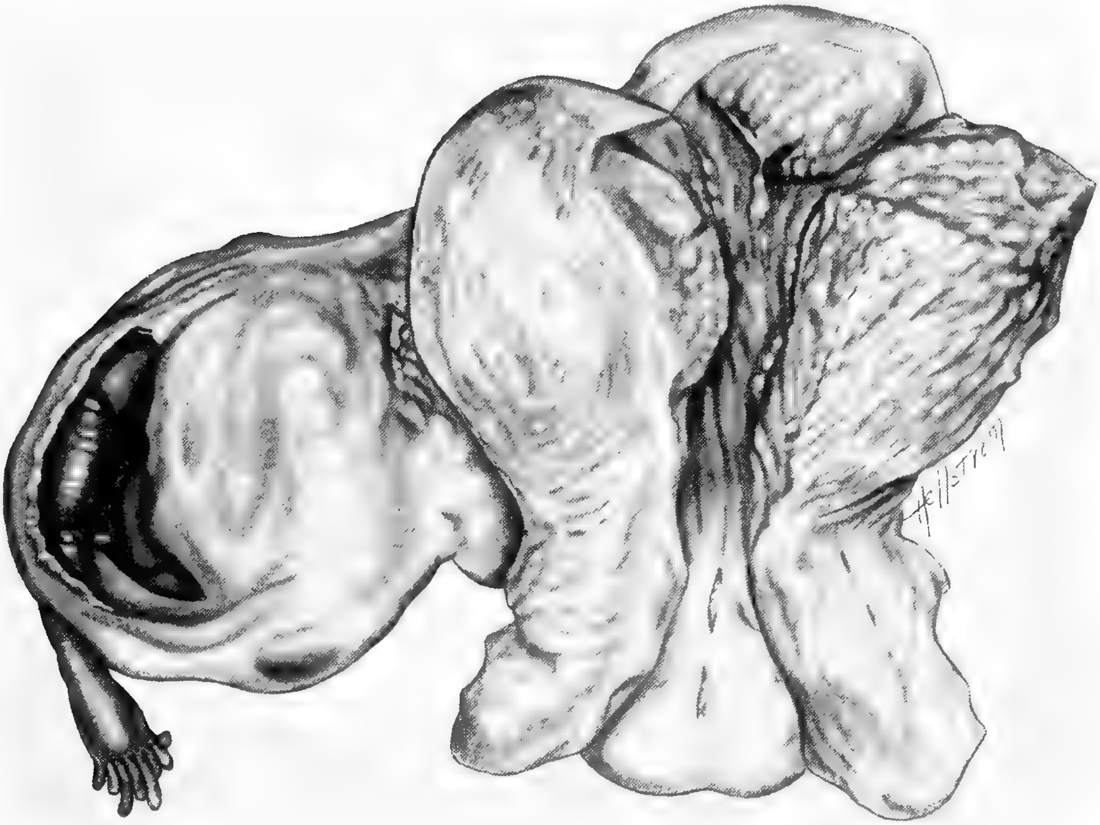


Fig. 124. Menorrhagia, prolonged profuse regular menstruating with marked anemia. Previous curettage showed marked decidua-like change, and gave no improvement. The endometrium is thick, shows late interval secretory changes and hyperplasic cystic glands. The ovary contains a corpus luteum cyst, presumably of temporary but likely recurrent nature.

MENORRHAGIA

Menorrhagia, or prolonged and profuse, but regular menstruation, also is a commonly occurring abnormality of function. If the duration is only five or six days and the flow excessive, the term menorrhagia may be applied. More often the duration of flow is eight to fifteen days, and the third to the sixth days, particularly are associated with profuse blood loss. This condition may cause marked anemia. More often the anemia appears gradually, apparently because the blood loss stimulates the marrow to more rapid ery-

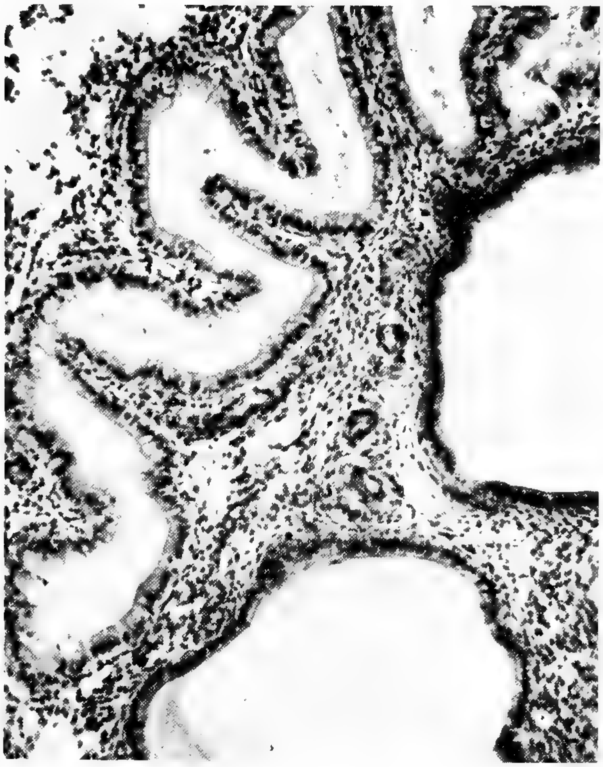


Fig. 125. Late interval secretory endometrium with cystic changes. In the left side of the photograph is the moderately tortuous typical late interval or early progestational type of gland showing the basal globules and some peripheral globules of glycogen. This is normal for about the eighteenth or twentieth day of the menstrual cycle. In the right side of the photograph there are dilated cystic glands some of which do show slight secretory effects, but for the most part there is non-secretory epithelial cells characteristic of endometrial hyperplasia. This patient had a corpus luteum cyst with menorrhagia. Probably there was hyperestrogenism associated with the progesterone secretion.

thropoesis, and the respite from bleeding, though only two weeks, allows improvement in the anemia. As the cycles are repeated, usually the anemia becomes obvious.

As a rule, the endometrium shows a well-developed secretory phase (premenstrual type) at the onset of bleeding. Apparently during the menses the endometrium is not shed readily, so that recognizable "corkscrew" glands may be removed by curettage on the tenth or twelfth day. This has been termed "irregular shedding." Apparently it is related to a prolonged corpus luteum activity, an action that should have ceased abruptly and completely two or three days before the onset of menstruation. The pituitary hormones that affect the corpus luteum must have continued to stimulate the ovary. The cause of this mechanism is unknown. While in the majority of cases with functional menorrhagia the endometrium shows the secretory change, on occasion there is no secretory effect, with apparent absence of the corpus luteum.

The cause of functional menorrhagia is not clear. Subclinical hypothyroidism seems a definite factor in many cases, and the administration of proper amounts of thyroid extract may be followed by normal menstrual flow. In a fair number of cases nervous tension and anxiety seem to have a causal relationship. In these instances the hypothalamus must be affected by the psyche.

Menorrhagia may not be functional (that is, related to the endocrine function alone), but may be caused by organic disease in the pelvic organs. The small submucous myoma may cause the most profuse bleeding and be most difficult of diagnosis. It may produce no obvious enlargement and may be missed with the curette. Adenomyosis of the uterine wall characteristically causes menorrhagia, and often dysmenorrhea. Enlargement of the uterus may be absent, and this diagnosis may be impossible. Hysterography may show the submucous myoma and may demonstrate in fifteen per cent of cases with adenomyosis the filling of the minute glands extending into the myometrium. Chronic pelvic inflammatory disease, endometriosis and other organic diseases may produce menorrhagia. If the diagnosis of an organic abnormality that may cause menorrhagia can be determined, then the menorrhagia is assumed to be secondary. At times the true diagnosis is clear only after laparotomy has been necessary because of continued profuse bleeding.

Treatment consists of thyroid extract when indicated, as determined by the history, physical examination and laboratory findings, and of mild sedation if necessary. Curettage is always performed if the bleeding continues longer than ten days, and not infrequently this procedure does help. On rare occasions, endometrial carcinoma is found. After curettage, testosterone propionate in 50 mgm. or 100 mgm. doses, may be given before the menses with improvement. Organic disease always is suspected. If the patient does not improve after the simpler treatments, and especially if she is in the older age group (after thirty-five or forty years of age), hysterectomy may be necessary.

DYSMENORRHEA

Dysmenorrhea, menstrual pain, has been classified as being of two types, primary and secondary. The latter is a symptom caused by organic disease, as cervical stricture, adenomyosis of the uterus, myomas of the uterus, salpingitis, adherent malpositions and external endometriosis.

But primary dysmenorrhea is the common developmental dysmenorrhea, experienced by all and much exaggerated in some young girls. This type of pain occurs only if ovulation has preceded this menstruation. For this reason many young girls have no pain in their first two years or so of menstruation. But progesterone has some necessary effect in sensitizing the myometrium, so that the muscle bundles must have increased spasm, similar to the spiral arterioles of the endometrium; or perhaps it is the arterioles themselves in the myometrium that develop the spasm, when the progesterone has been metabolized and excreted.

Another important factor is the development of the uterus. As long as the uterus remains of adolescent size, the pain continues. When it has reached full normal size, at the age of twenty-three or twenty-five years, the pain disappears although ovulation and progesterone secretion continue.

The narrowness of the cervical canal seems a factor at times; dilation may be helpful, though usually only for a few cycles.

Acute anteflexion of the uterus seems related occasionally, and may be treated by dilatation of the canal and insertion of a stem pessary for six weeks, if the symptoms are entirely incapacitating. This is rarely indicated; the stem pessary occasionally causes pelvic infection, involving the tubes or parametrium.

The psychogenic factor raises its head again, and here it undoubtedly is important. Premenstrual tension, exaggerated by various emotional conflicts and the mounting fear of impending menstrual pain, certainly paves the way for an emotional upheaval. Extreme nervousness may be obvious and degrees of hysteria may develop. Many fears of the "curse" are well nurtured by stories of severe pain before the menarche, made more emphatic by overly sympathetic mothers, aided by an inherited unstable nervous system, and even abetted by the physician who "knocks her out" with morphine or demerol. Psychologic maladjustment is very frequent in patients with severe primary dysmenorrhea.

Treatment depends most importantly on careful explanations of the nature of menstruation, and the tension factors in an individual case. The patient is encouraged not to let menstruation interfere with the normal physical activities of life. Exercises, at the onset, such as bending and stretching to pick up small objects from the floor and place them on a high shelf, seem helpful, probably by their psychogenic effect. Premenstrual mild sedation, as with phenobarbital, grains one-fourth three times daily, and cramp sedatives, such as edrisal (dexedrine, aspirin, and phenacetin, with or without codeine sulfate), or capsules containing aspirin grains three, phenacetin grains three, codeine sulfate grains one-half, and atropine sulfate grains one-hundred and fiftieth, give satisfactory results in the majority of cases. Small doses of estrogens, such as Premarin 0.6 mgm., may be given daily between menses, and may have slight growth effect on the uterus. Thyroid extract may be prescribed; it seems important in increasing the growth of the hypoplastic uterus. Dramamine or thorazine by mouth or by rectal suppository may be helpful for nausea or vomiting. One should hesitate to give morphine, demerol or similar opiates, because of the tendency to addiction. Similarly, although alcohol is effective, alcoholism can develop.

Dilatation and curettage, or dilatation and insertion of the stem pessary seem necessary occasionally. Division of the nerves carrying the pain sensations from the uterus has been performed since 1925 (Cotte) by excising the hypogastric plexus over the promontory of the sacrum, and more recently by Doyle by dividing the uterosacral ligaments widely. But these major operations (even though the latter may be performed through the vaginal approach) are rarely necessary, and as a rule should not be used unless there is complicating pelvic pathology. The major associated pathology of secondary dysmenorrhea is endometriosis, with its very painful implants in the cul-de-sac and on the uterosacral ligaments. Severe chronic inactive salpingitis may also cause marked pain, and major surgery with excision may be necessary in this instance. At times a patient is thought to have no pathology in the pelvis, but later proves to have a submucous myoma, adenomyosis of the uterus or non-palpable endometrial implants on the pelvic peritoneum. Hyponotism has been employed by some exponents of this therapy, with reported good results.

Estrogen or testosterone, given orally or intramuscularly several days before ovulation should occur and repeated until near menstruation, has been used to inhibit ovulation. This treatment does prevent menstrual pain, but on repeated use ovulation tends to break through and occur in spite of the hormone, unless a large dose is given or the dosage is increased. The results are strictly temporary, the dysmenorrhea recurring with subsequent cycles. This unphysiologic method is useful only for its psychological and temporary relief from pain.

Since most cases with dysmenorrhea are cured spontaneously with maturity of the sexual organs (by the age of twenty, twenty-two or twenty-five years), understanding, sedation and temporizing are the usual procedures. Rare cases with extraordinary pain may present quite a problem.

ADENOCARCINOMA OF THE ENDOMETRIUM

Adenocarinoma of the endometrium is one of the more important diseases in gynecology. Just as all malignant tumors are of vital importance to every patient, this neoplasm, both because of its frequency, and because the symptoms associated with it are so often discounted as being due to common menopausal irregularities, has many intriguing characteristics. Its importance is attested by the numerous publications on the subject. This tumor arises from the glands of the endometrium, and not the stroma. The latter occasionally forms a malignant growth known as endometrial sarcoma. The many and interesting characteristics of endometrial carcinoma will be enumerated in the following discussion.

The incidence of adenocarcinoma of the endometrium seems to be increasing. This change is not readily explained. Some thirty or more years ago well documented statistics indicated that about eight carcinomas of the cervix occurred to one carcinoma of the endometrium. A little later the incidence seemed to be about five carcinomas of the cervix to one carcinoma of the endometrium. In recent years the incidence has seemed about two to one, and finally some very recent articles have indicated approximately equal occurrence of carcinoma of the cervix and carcinoma of the endometrium. Does this mean that the incidence of carcinoma of the cervix is being reduced? It may well be be-

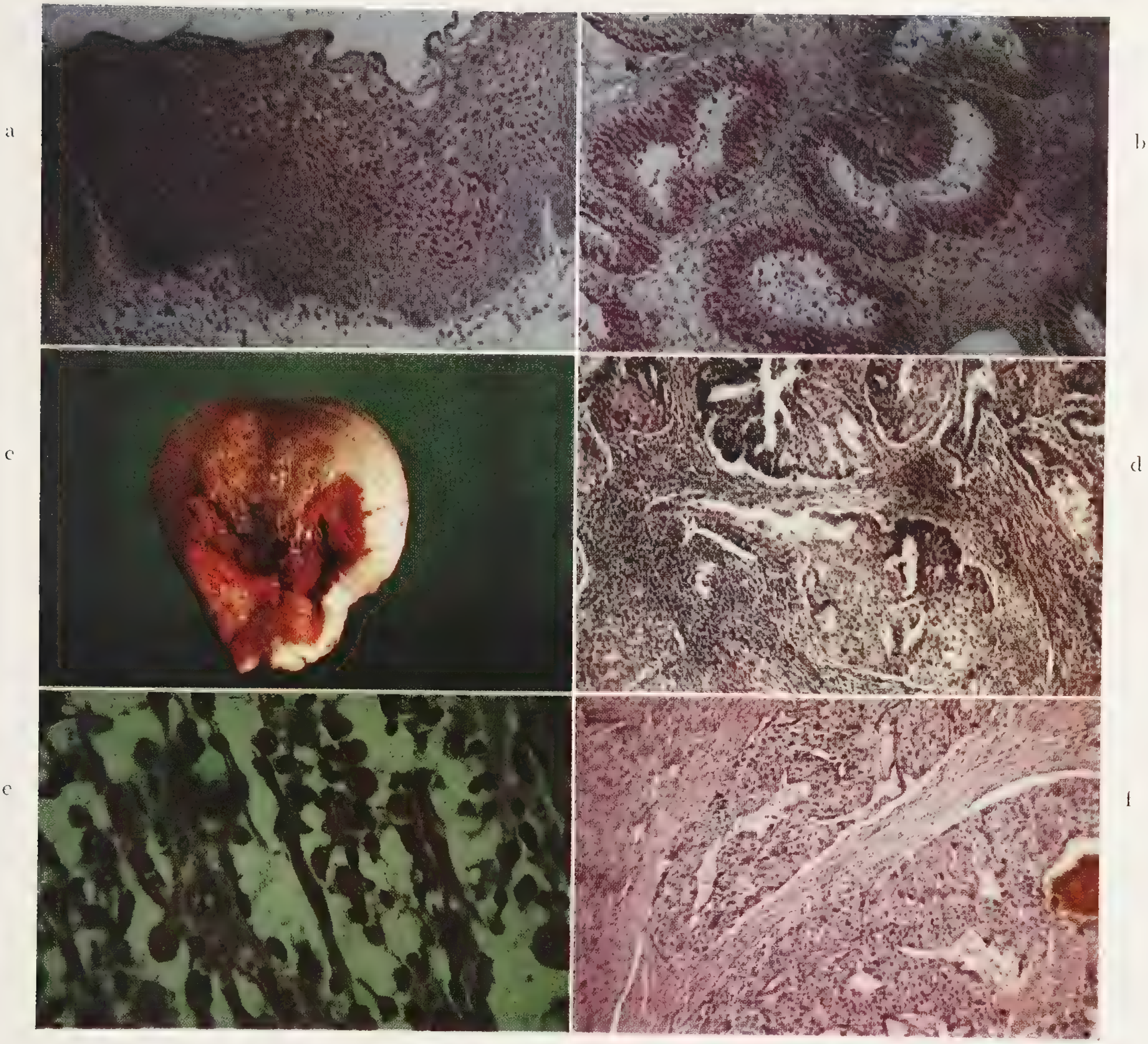


PLATE IV

a. Normal squamous epithelium from the external cervix, stained with Best's carmine stain for glycogen. The glycogen forms in the more mature squamous cells, and is shed with them into the lumen of the vagina. The Schiller test depends upon the presence of glycogen, the iodine reacting to form a brown color. The glycogen is of great importance in the normal acidity and normal flora of the vagina.

b. Late interval secretory endometrium of about the twentieth day of the menstrual cycle, stained with Best's carmine. The basal globular, appearing as a clear space in the H. and E. sections, stain red. Some of the glycogen is pressing around the nuclei into the periphery of the cells, and already is being extruded into the lumen.

c. Large firm endometrial polyps, which have extended deeply into the wall of the uterus. This may represent one form of stromal myosis. Patient, age 22 years, had had repeated severe hemorrhage. Microscopic shown in Figure 131.

d. Adenocarcinoma of endometrium. While the glandular pattern is obvious, the more solid appearance of half of the tumor indicates increased malignancy, interpreted as grade 2. The nuclei show variation in size and shape, and increased mitoses. Another marked chronic inflammation results from infection in the growth, which acts as a foreign body.

e. Malignant mixed mesodermal tumor of the uterus. The great variation in size, shape, and appearance of the cells suggests sarcoma. The central elongated cell shows striations. Ordinarily small abnormal glandular structures occur through the tumor.

f. Choriocarcinoma. The broad bands of malignant trophoblast, composed of both Langhan's cells and syncytium, are invading deeply into the wall of the uterus.

cause of the rather extensive treatment of chronic cervicitis, and because of the increased number of total hysterectomies being performed, which also removes the segment of the statistics of carcinoma of the cervix occurring in the cervical stump, (in the past, the stump left after subtotal hysterectomy has comprised from five to seven per cent of the total cases). Perhaps the results of the Papanicolaou cytology studies, the interest in biopsies of eversions of the cervix, and the discovery and treatment of carcinoma-in-situ, may have diminished the incidence. Certainly this is to be expected in the future, as the cytology studies are extended to more and more women of the population. Or perhaps there is some change in the metabolism of women in this present generation. One would immediately suspect that the wide usage of estrogenic hormone for therapeutic effects is a possible causative factor in the increased incidence of adenocarcinoma of the endometrium. Yet as one sees individual cases, it is certainly not impressive that any appreciable number of the patients with carcinoma of the endometrium have had treatment with estrogenic hormone.

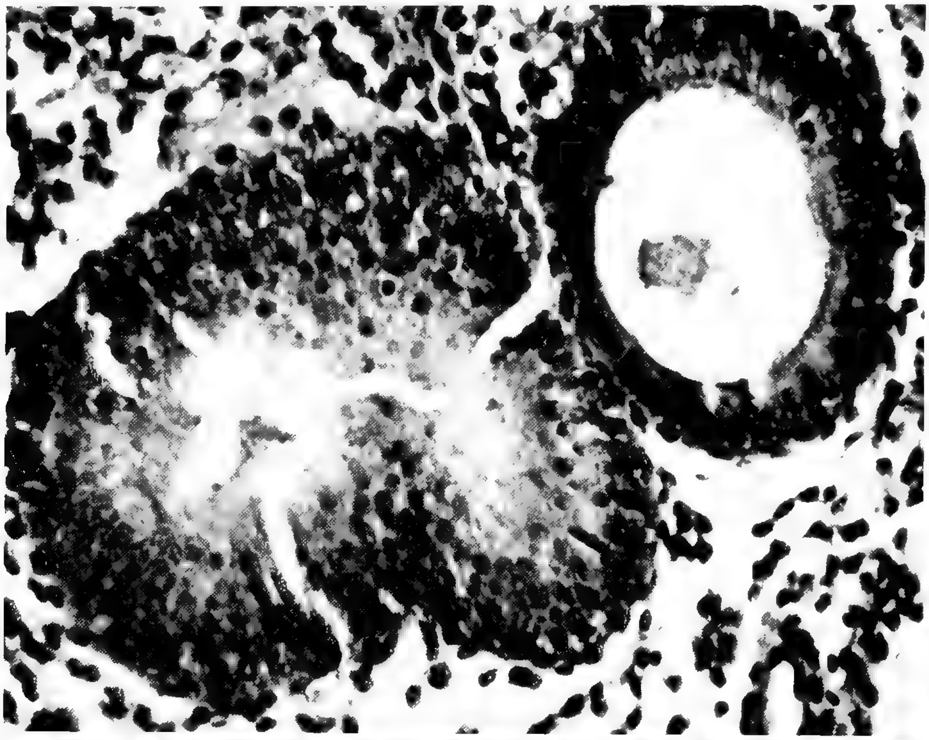
The incidence from another point of view in regard to the age of the patient probably has not changed in the past thirty years, as about eighty or eighty-five per cent of cases occur after the menopause, or at least in the menopausal years, while at least fifteen or twenty per cent occur in premenopausal years. The average age of occurrence is about fifty-five years. One must remember the tumor may readily occur between the years of forty and fifty, that it has been reported many times between thirty and forty years, and that it is not unknown between the ages of twenty and thirty. On extraordinary occasions it may occur in infants or young children. Similarly, in order to make the percentage average at age fifty-five, this tumor does occur in the quite elderly patient.

For a long time it has been known that adenocarcinoma of the endometrium particularly occurs in the obese patient, in the patient with diabetes, in the patient with hypertension, and finally in the patient with a late menopause. While this would seem to isolate a very separate group in which to look for adenocarcinoma of the endometrium, and while these four findings occur in greater incidence than women in general, yet by no means do the majority of patients have these four findings or even any one of them. The patient may be quite thin, may have normal or low blood pressure, no suggestion of diabetes mellitus, and may have had a very early menopause in the thirties or early forties.

The pathology of carcinoma of the endometrium has many deviating avenues of approach and study. The tendency has been to classify the tumors microscopically as Grades 1, 2, 3 and 4. In the Grade 1 adenocarcinoma, the glands are "back to back" with little or no stroma between them, and the cells lining the glands are piled up two or three layers deep, usually show no evidence of secretion, being similar to those cells found in the glands of endometrial hyperplasia with hyperestrogenism, but with moderately increased cellular atypias, with increased number of mitoses and with abnormal mitoses. These changes appear to be an accentuation of those found in the benign endometrial hyperplasia. The picture is characteristic, definite, and has been labelled "adenoma malignum" in the past, to indicate its relatively low grade of malignancy, although it is not to be discounted, because it may be just as fatal in its relatively slow growth as any malignant tumor. The results after excision of this Grade 1 tumor are particularly gratifying.

Grade 2 adenocarcinoma shows lesser degrees of differentiation, and there are some areas of solid masses of tumor cells which extend into the stroma about the glands and which pile up inside the glands. This more solid appearance of the proliferated tumor cells is definitely in minor degree in the Grade 2 carcinoma. The degree of malignancy is thought increased in this grade. The ma-

Fig. 126. Atypical endometrial hyperplasia. The marked overgrowth of the epithelial cells which are piled up in large degree and show increased mitoses may represent one form of atypical hyperplasia. On the other hand this change may be due to the peculiar cut of the gland with so-called tangential section, in which many of the cells are cut across due to the peculiar angle.



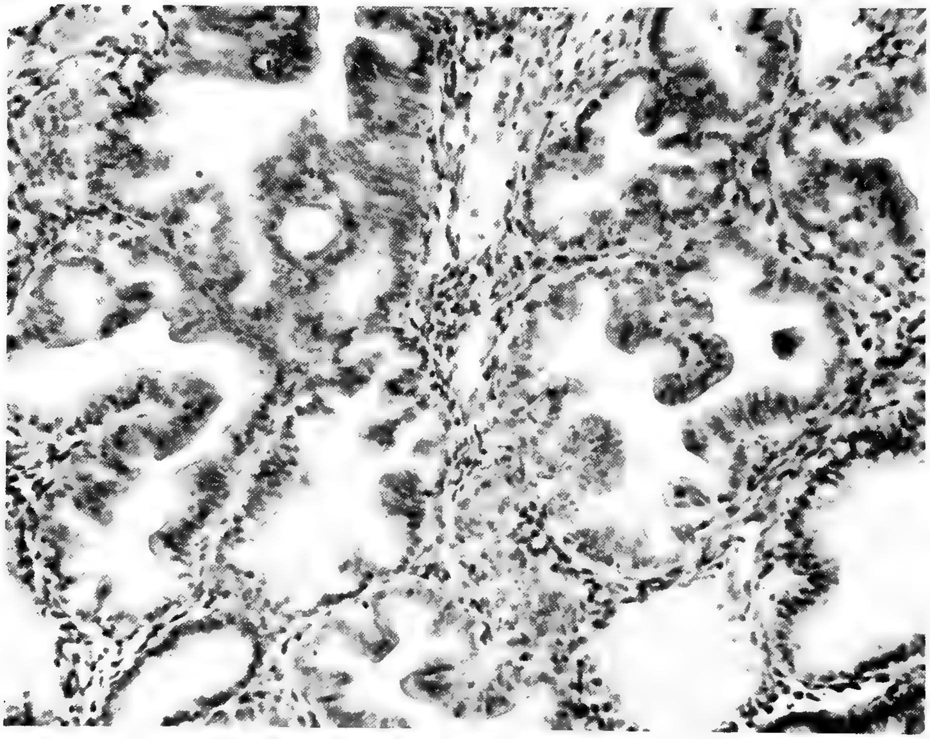


Fig. 127. Atypical hyperplasia with adenomatous appearance, papillary infolding of glands and piling up of cells. A few glands at the periphery show a normal late interval secretory pattern.

jority of carcinomas of the endometrium fortunately do fit into Grades 1 and 2, being relatively slowly growing and slowly metastasizing. Grade 3 shows a much larger extent of undifferentiated tumor cells, particularly showing less of the adenomatous appearance and more of the solid masses of tumor cells, with intermingled glands which are also malignant. The Grade 3 adenocarcinoma is considered much more malignant than the Grades 1 and 2 tumors. It extends more rapidly and is more sensitive to irradiation therapy. The cure rate by any method or combined methods is less than that in Grades 1 and 2.

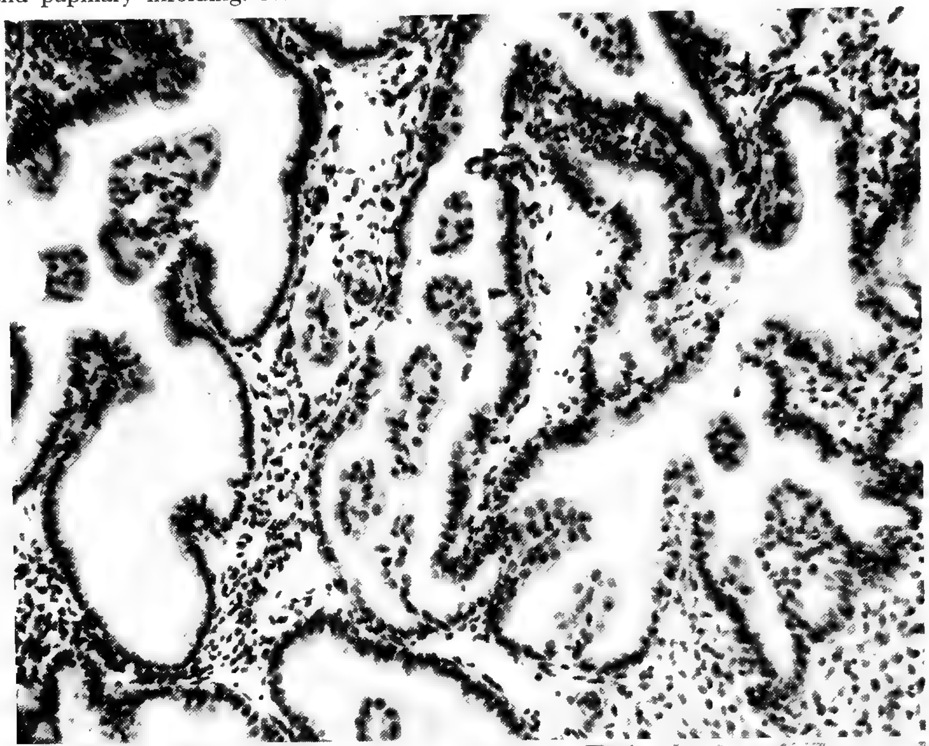
Grade 4 adenocarcinoma of the endometrium is relatively rare, probably making up only three or four per cent of the cases. In this instance there are very few typical gland formations in the tumor, as it is made up of almost entirely solid masses of tumor cells, which are very undifferentiated, do not simulate the adult gland cells in any degree, and have increased numbers of mitoses, many of which are abnormal. This appears to be a very malignant tumor, sometimes difficult to differentiate from squamous cell carcinoma of the cervix. These tumors grow rapidly before they are discovered, and although radiosensitive to quite a satisfactory degree, commonly have spread beyond the uterus or metastasized beyond the possibility of cure in a considerable percentage of cases with this uncommon form of adenocarcinoma. The excised uterus after irradiation therapy in the Grades 3 and 4 types of adenocarcinoma may show no residual carcinoma in the majority of cases, and yet the patient may have a fatal outcome from the metastases which occurred so early.

The gross staging of adenocarcinoma of the endometrium has been attempted by a number of authors (Miller, Schmitz and others), but none of their suggestions have been widely accepted, certainly not to the same degree as is the acceptance of staging of carcinoma of the cervix. Recently, Blaikley, Kottmeier, Martins and Meigs (1958) have suggested that stage 1 adenocarcinoma of the endometrium represents carcinoma confined to the corpus; that stage 2 represents involvement of the corpus and the cervix; that stage 3 represents extensions into the parametrium, but not outside the pelvis; and finally that stage 4 represents metastases outside the true pelvis, or extensions into the bladder or rectum. Undoubtedly, it is most important to understand the types of cases with which one is dealing in order to make a prognosis and to understand the life history of the particular tumor.

The cure rate of Grade 1 adenocarcinoma of the endometrium in the very early stage should approximate between ninety and one-hundred per cent, whereas the Grade 4 adenocarcinoma which has extended beyond the uterus will have a cure rate of almost zero per cent. It is only if one has a breakdown of the types and stages of the carcinoma that one can evaluate various methods of treatment and decide the best method for the individual patient. This has rarely been done, as most of the reports consider over-all percentages.

Adenocarcinoma of the endometrium often has been called carcinoma of the fundus of the uterus. Perhaps this is because a sizeable percentage of the cases do arise in the true fundus of the uterus, the portion of the uterus between the orifices of the two Fallopian tubes. This area may represent the site of origin of the majority of cases of adenocarcinoma. However, this growth certainly may originate in the anterior or posterior wall or occasionally down near the endocervix. This papillary tree-like neoplasm tends to grow and spread over the entire endometrium. The diffuse arrangement would seem to be a matter of time, allowing its spread along the endometrium and not a spontaneous origin from the entire endometrium simultaneously. It is well known that adenocarcinoma may begin in endometrial polyps, but as to how often these polyps represent the origin of

Fig. 128. Adenomatous hyperplasia (atypical hyperplasia). The glands are close together, have various ramifications and papillary infolding. Note the central cells are pale. Patient subsequently developed adenocarcinoma.



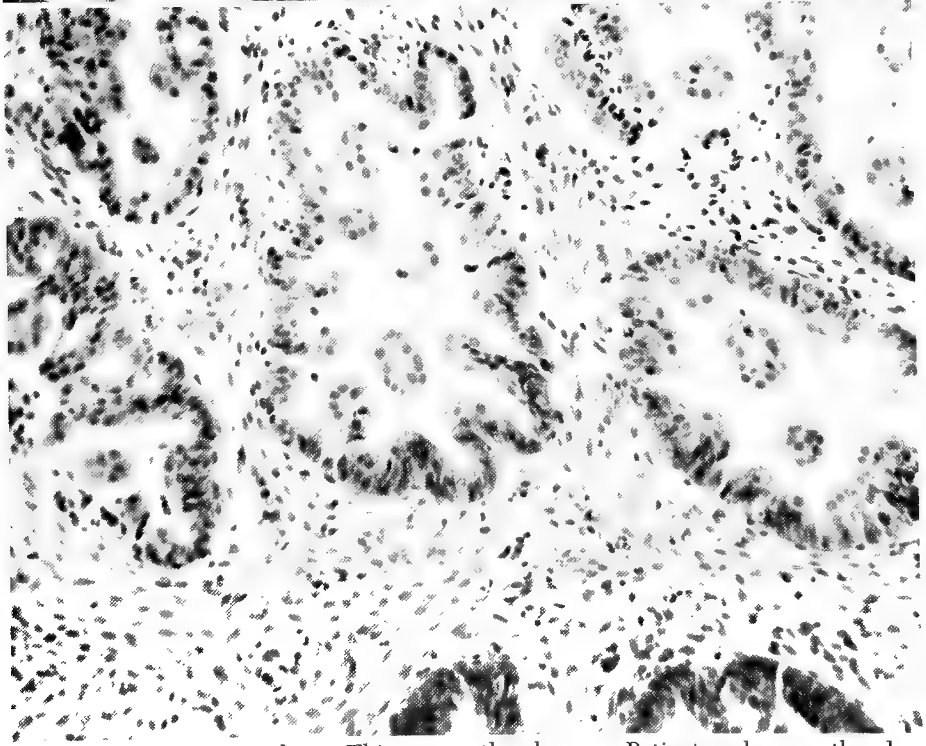


Fig. 129. Atypical endometrial hyperplasia. This area is characterized by papillary infolding of glands. Note the pale appearance of the cells extending into the lumen. Patient subsequently developed adenocarcinoma.

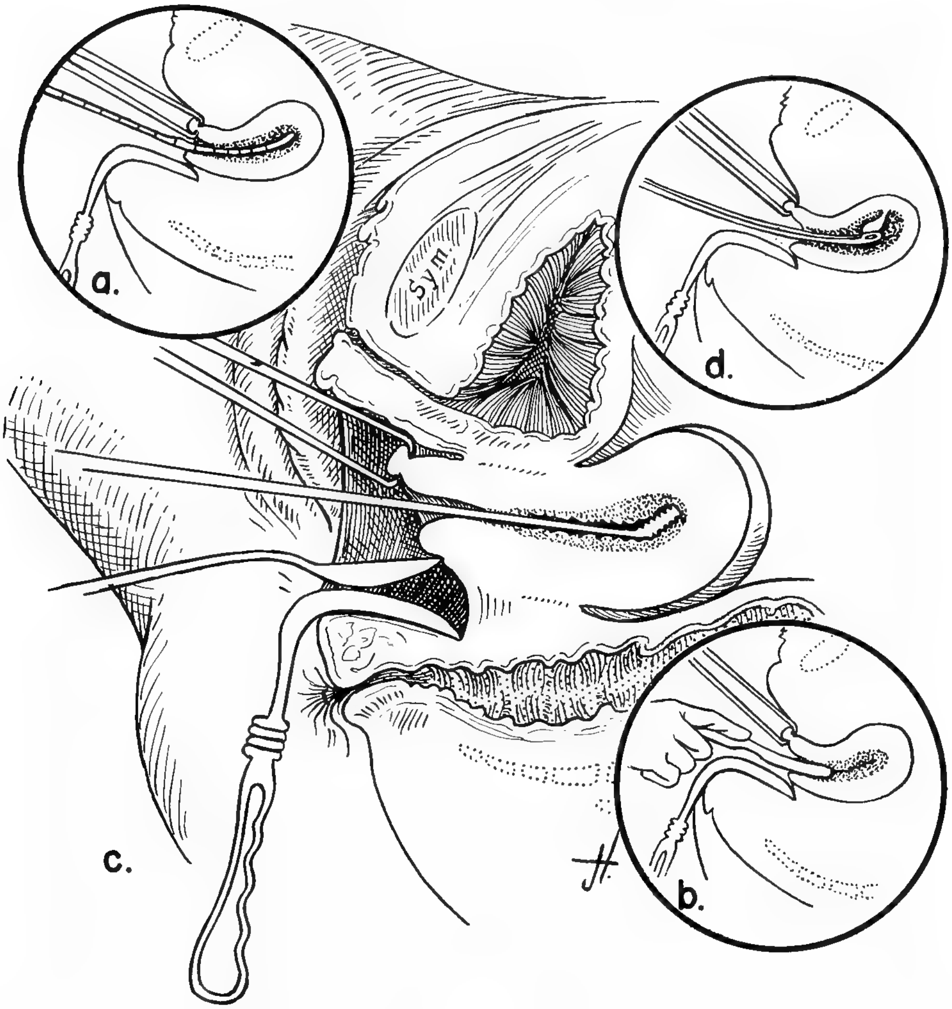


Fig. 130. Dilatation and curettage of the uterus.

a. Posterior retractor inserted, anterior lip of cervix pulled down with tenaculum, and the uterine cavity is measured accurately.

b. The canal is dilated with Hegar dilators, 8 to 10 mm.

c. The cavity is curetted systematically, covering anterior, posterior and each side wall, and across the fundus. The Kelly serrated curette is illustrated. The spoon may be used, or more recently telfa gauze, which absorbs the blood and leaves the curettings on the smooth surface.

d. The polyp forceps always follow the curette. The Randall ureteral stone forceps remove a surprising number of polyps.

endometrial carcinoma is unknown.

Endometrial polyps are relatively frequent in occurrence, in the premenopausal woman often causing a slight intermenstrual bleeding. They are found frequently in hysterectomy specimens, with no particular symptoms related to the polyps. In the postmenopausal uterus, of which so many are seen in the present vogue of vaginal hysterectomy, a considerable percentage contain polyps, some of which are quite large, two or three or more centimeters in diameter, and associated with no abnormal bleeding or symptoms of any kind. It is our impression that fifteen or twenty per cent of postmenopausal uteri contain endometrial polyps, whereas a much smaller number of postmenopausal uteri develop adenocarcinoma. It is doubtful that more than a small percentage of all adenocarcinomas of the endometrium do arise in endometrial polyps.

The adenocarcinoma of the endometrium,

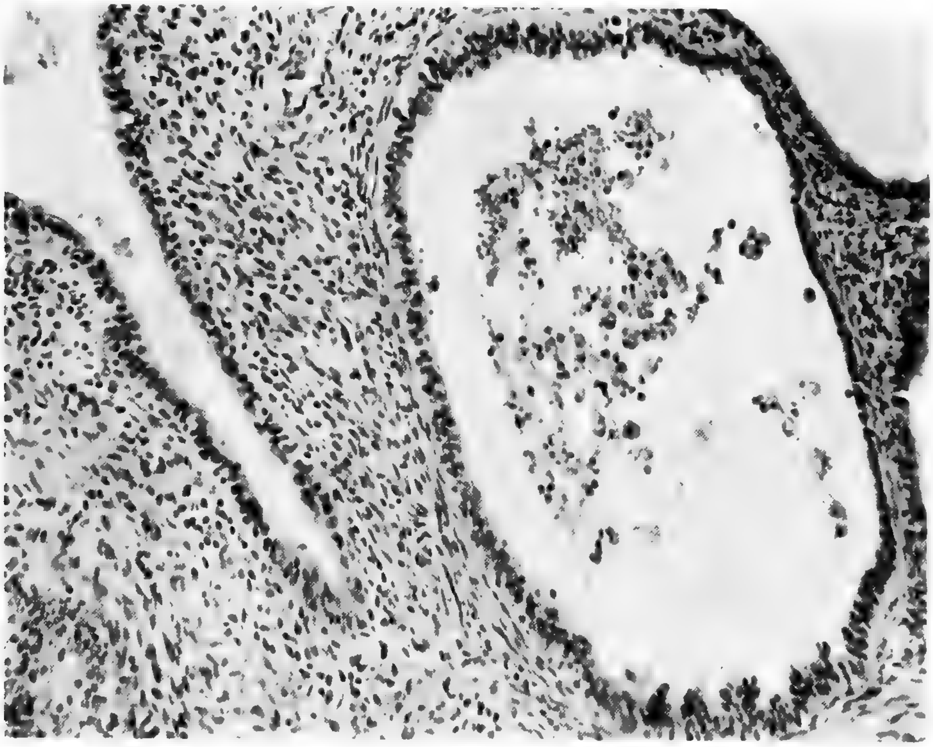
which in the majority of cases is of Grade 1 or Grade 2 character, may remain in the uterine cavity for many months, or two or three years, before spreading outside the uterus. Those tumors showing higher grade malignancies may spread earlier. After the tumor has become quite well-formed in the endometrial cavity, there begins extension into the myometrium. Often this is of relatively slight degree, in other cases of moderate degree, and of course, with sufficient time the growth may extend entirely through the serosa of the uterus, perforating the peritoneum and spilling cancer cells into the cavity. There may be many small areas of perforation in an individual uterus.

One of the first destinations of metastasis of endometrial carcinoma is the ovary. While some reports have indicated that only about five per cent of cases have metastasis to the ovary, several other reports have indicated that fifteen to eighteen per cent of all cases will have some tumor present in one or both ovaries, if carefully sectioned. Thirty years ago Sampson suggested this occurrence might develop because of retrograde flow of the cancer cells through the fallopian tubes with subsequent implantation on the surface of the ovary. More often the metastasis is situated in the interior of the ovary, which suggests a lymphatic spread. It is well-known that the lymphatics of the uterus extend alongside the Fallopian tubes to communicate with those of the ovary. Fortunately in some cases metastases in the ovaries represent the only spread in the individual case, and cure may follow excision of the uterus, tubes and ovaries. This phenomenon and occurrence make it entirely necessary that the operation always be a complete one when endometrial carcinoma is present. The tumor extends by way of the parametrium into the broad ligaments and the uterosacral ligaments and causes palpable induration after a period of time. When present, this reduces the percentage of cure very materially.

The tumor also metastasizes along the lymphatics to the sacral nodes, the obturator and hypogastric lymph nodes, and up into the aortic nodes. Positive nodes have been found in fifteen to twenty per cent of cases. The metastases may extend to the liver, the lungs, the cervical lymph nodes, and elsewhere. Death may occur from toxicity and metastases, and the cachexia associated with it, from uremia after interference with the urinary drainage, from interference with other vital organs, such as the liver, and from hemorrhage from the uterus itself.

While the vast majority of adenocarcinomas of the endometrium are of the nonsecretory type, seemingly akin to the epithelium of endometrial hyperplasia, a small percentage of these tumors shows a very definite secretory form. Here the cells may be more rounded, more swollen, and show vacuoles in the cytoplasm. This does not mean that there is a luteal effect in this minority group of patients at that particular time. It does bring up the point that the majority of patients with adenocarcinoma of the endometrium are not ovulating or forming a corpus luteum at the time the tumor has developed or after its development. Naturally this is true because most of the cases are menopausal or postmenopausal, and one does not expect ovulation, especially after the menopause. However, Brewer and Jones have shown that in younger women there may be associated ovulation and formation of the corpus luteum, with secretory endometrium adjoining the adenocarcinoma. The absence of ovulation and the corpus luteum hormone is not a prerequisite to the formation of adenocarcinoma of the endometrium. This would refute to some extent the theory that unopposed estrogen may be a cause of endometrial carcinoma. Of course, the estrogenic theory is supported and enhanced by the very frequent finding of endometrial hyperplasia associated with adenocarcinoma of the endometrium, but the majority of patients with this very commonly occurring lesion of en-

Fig. 131. Endometrial polypi of extreme degree showing a hyperplasia pattern of the glands with cystic dilatation and piling up of cells and a very fibrous type of stroma. This lesion has extended deeply into the wall of the myometrium and may represent a polypoid form of stromal endometriosis.



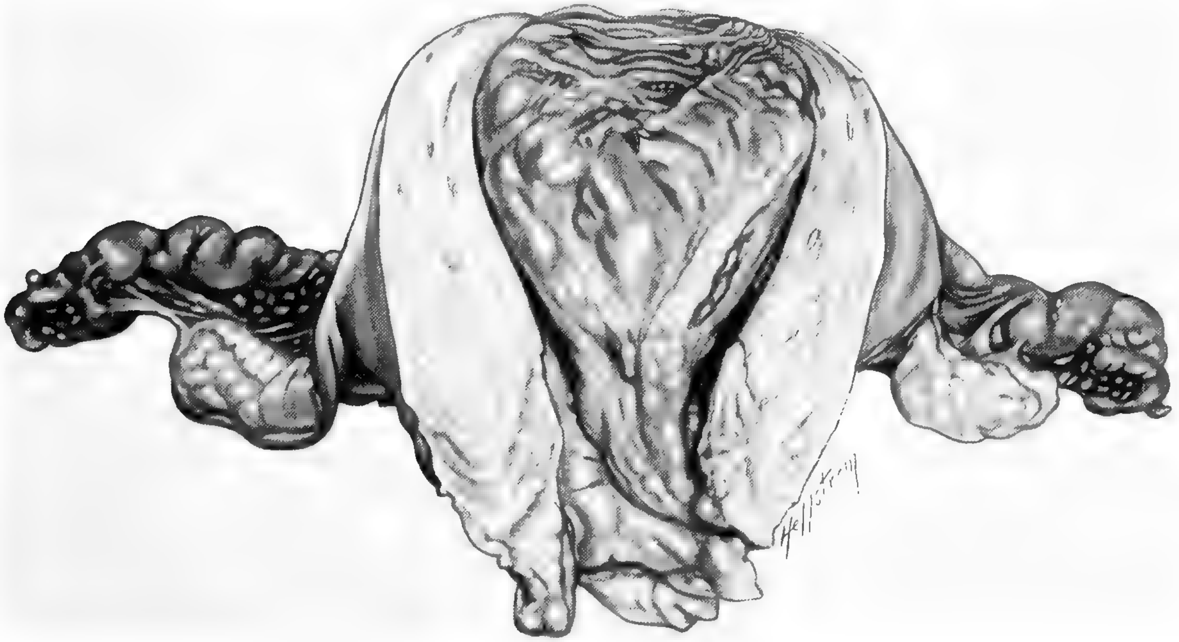


Fig. 132. Endometrial polyp of unusually large size. Patient had menopausal menorrhagia and was thought clinically to have myomas of the uterus. The polyp had a meaty, dark red appearance, and was entirely benign.

dometrial hyperplasia do not have adenocarcinoma.

At least, it is true that the occurrence of endometrial hyperplasia in the premenopausal women is not to be considered a precancerous lesion. On the other hand, in the postmenopausal woman, true endometrial hyperplasia has been found associated with adenocarcinoma of the endometrium in a sizeable percentage of cases. This was first pointed out by Novak and Yui, and has been confirmed by several other investigators. Some have felt that the finding of endometrial hyperplasia postmenopausally is of serious prognostic importance, possibly representing a precancerous lesion. As a rule, however, one would treat these patients with curettage and observe them for recurrent bleeding; one would consider hysterectomy if there was recurrent bleeding. If there are atypical changes in the hyperplasia the prognosis probably is more serious.

The association of the granulosal cell tumors of the ovary, the estrogen producing tumors, with endometrial hyperplasia, which occur in the prepubertal child, during menstrual life, and postmenopausally, is well known though infrequent. Of particular interest is the simultaneous finding of adenocarcinoma of the endometrium. About ten per cent of all patients with granulosal cell tumors of the ovary also have endometrial carcinoma. While some have suggested that this represents a pure coincidence of two tumors, one can hardly ignore the association, and it seems doubtful that it could be coincidental in either direction. Neither tumor is that frequent, particularly the granulosal cell tumor

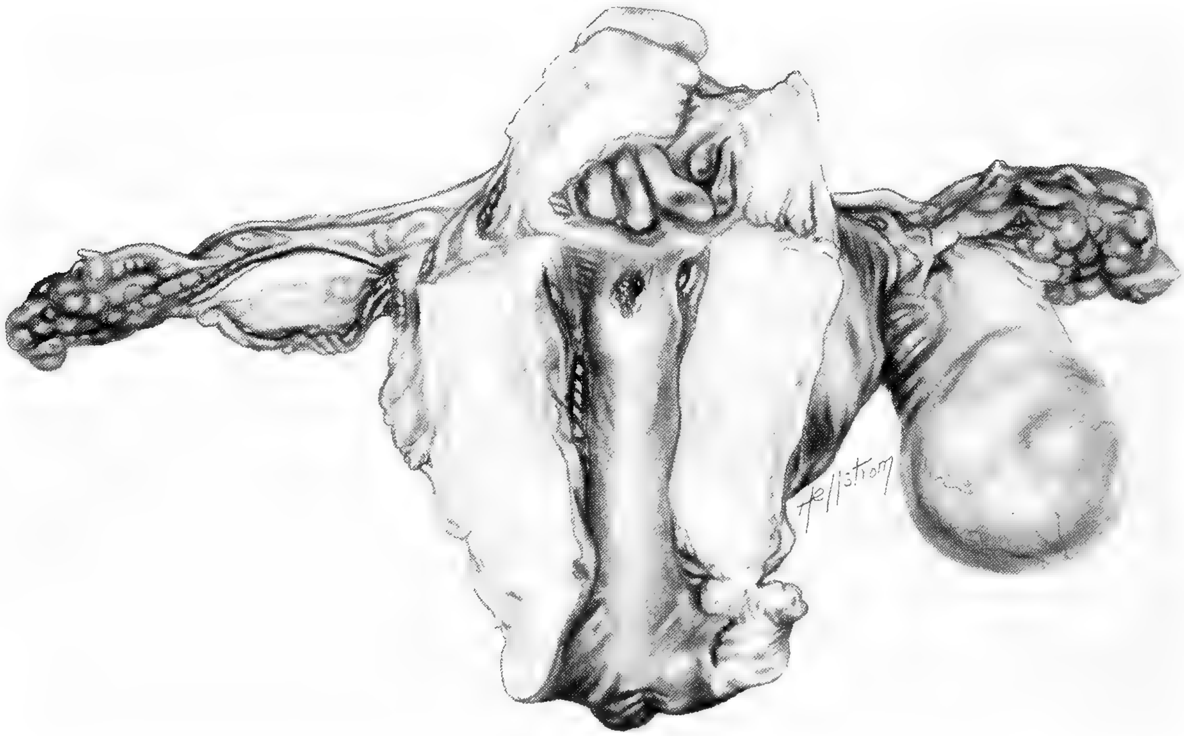


Fig. 133. Multiple endometrial polyps in the fundus of the uterus. Quite frequently occurring, may produce slight intermenstrual bleeding or postmenopausal bleeding. This patient, age fifty-five years, had received estrogenic hormone in small doses continuously for five years. A small, benign, functionless serous cyst is present in the right ovary.

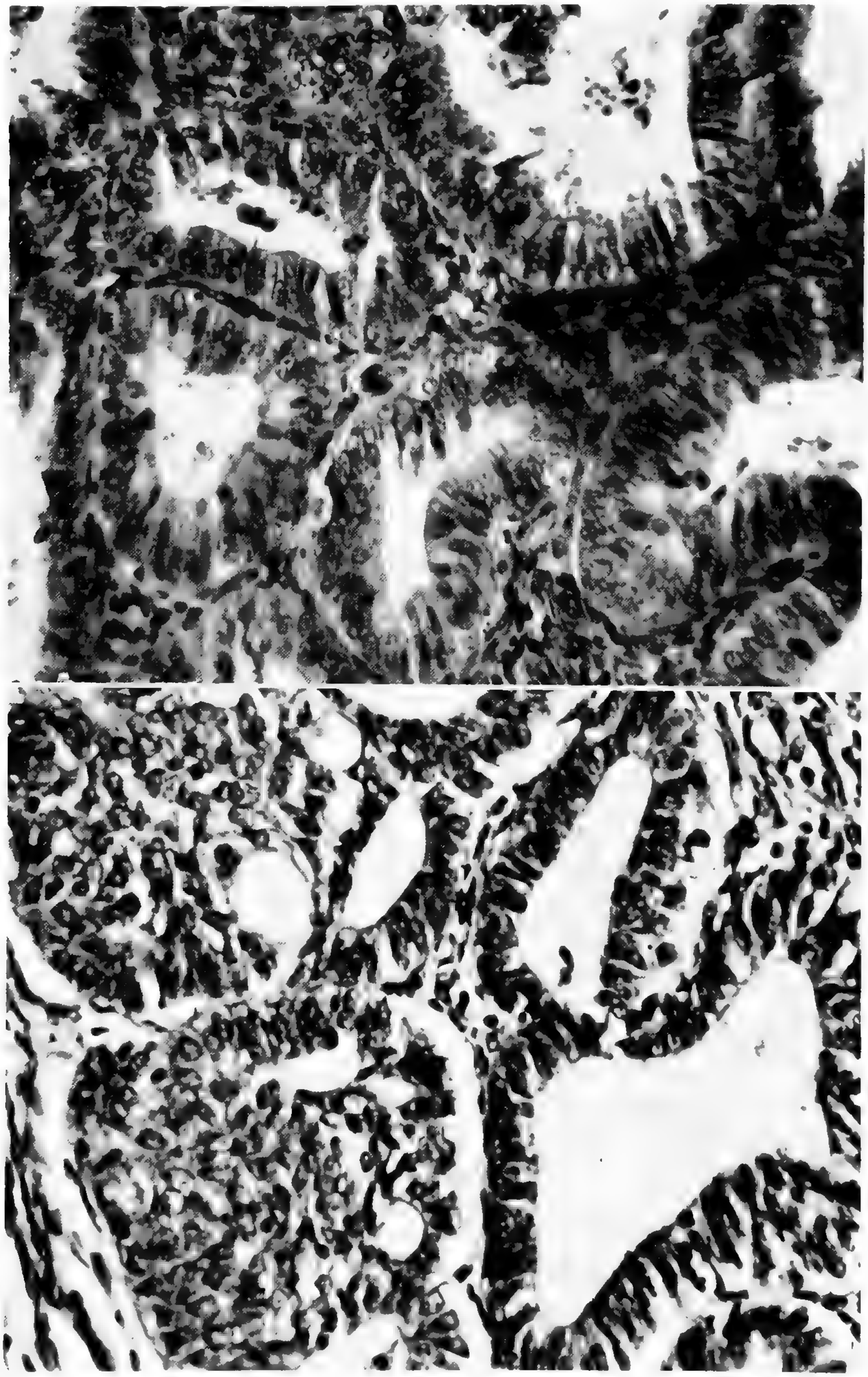
of the ovary. It does seem that endometrial hyperplasia occurring postmenopausally does have some relation to adenocarcinoma of the endometrium, and hyperplasia is produced by the granulosal cell tumor.

Of all the millions of women who have received, or are receiving estrogenic hormone, a very few reports of the development of adenocarcinoma following estrogenic therapy have appeared in the literature, probably no more than twenty. If estrogenic therapy is carcinogenic, then with the extraordinarily common use of this hormone, one would expect a rather frequent development of endometrial carcinoma. On the other hand, there are certainly remarkable changes in the endometrium which occur after prolonged estrogen administration. In the first place, benign and typical endometrial hyperplasia, with its "swiss-cheese" gland and hyperplastic epithelium, with some piling up of the epithelium, is a frequent finding after prolonged estrogenic therapy. In some cases there are atypical changes in this endometrial hyperplasia with some extension of the epithelium into the stroma, some piling up of the epithelium to an unusual degree, and abnormal changes in these cells. In addition, the adenomatous changes (localized areas of the glands being very closely packed together) may make one suspect the very early phase of adenocarcinoma. Apparently these quite unusual and somewhat alarming findings may regress to normal after removal of the estrogenic stimulus by discontinuing the therapy. But, with increasing experience and observation, one cannot help but be concerned to some degree with these endometrial changes which develop after prolonged estrogenic treatment; probably carcinoma develops in a minor percentages of these cases. A few years ago it was reported (Randall) that adenocarcinoma occurring after the menopause was associated with a thick vagina, indicating a full estrogenic effect, which was interpreted as meaning that adenocarcinoma developed when estrogen from endogenous sources was present. Since then it has become evident that in the majority of cases with adenocarcinoma of the endometrium, the vagina is thin, desquamating immature parabasal cells which show no evidence of estrogen stimulation. Certainly this is true in most of the elderly patients, but by no means all of them.

Some ten years ago Smith, followed by other investigators in Boston, reported that stromal hyperplasia in the ovaries is associated with adenocarcinoma of the endometrium. The stromal cells in the cortex were found enlarged, more prominent and were thought possibly to have some hormonal activity. It has been suggested that these cells may produce estrogen which may be a factor in the causation of adenocarcinoma of the endometrium. Other investigators (particularly Green) have indicated that stromal hyperplasia is an inconstant and unrelated finding. Since the majority of patients have had preoperative irradiation in the case of this tumor, one wonders if the material may not show artefactive changes after such therapy.

In the past the increased incidence of associated myomas of the uterus with adenocarcinoma has been pointed out on many occasions, and it has been suggested that they may be related to hyperestrinism. Because myomas apparently do not arise if the ovaries have been excised, and the uterus left intact, and because myomas do regress in size after the normal menopause, it is evident they are dependent on estrogenic hormone. Similarly it has been stated that adenocarcinoma of the endometrium does not develop if the ovaries have been removed and the uterus has been left in place. On the one hand it is doubtful that the association of the myomas at this age has any direct relationship because of their great frequency anyway. Secondly, the operation of bilateral oophorectomy without hysterectomy is so uncommonly performed, that very few cases are available for any statistical study. It is of interest that Cianfrani reported twelve cases of postcastration adenocarcinoma of the endometrium. He must have had a considerable series of cases with bilateral oophorectomy to find this number with carcinoma in the uterus.

Adenoacanthomas of the endometrium are reported with great variability and frequency in various localities. This mainly is because of the interpretation of different pathologists. The adenoacanthoma was originally described as a mixture of adenocarcinoma and squamous



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cell carcinoma. In rare instances in the cervix, in the endometrium, and in other areas of the body, there may occur tumors that seem to have truly two types of malignant cells present, but the tendency is to believe the tumor is primarily an adenocarcinoma with metaplasia, developing squamous-like cancer from the adenocarcinoma. Squamous metaplasia associated with adenocarcinoma of the cervix, of the endometrium, or of the ovary, in which the metaplastic cells do not appear particularly malignant, is much more frequent, usually being associated with a lesser degree of malignancy, as Grade 1 or Grade 2. Tumors with this appearance have been reported recently in the ovary, associated with endometriosis of the ovary; the finding of this type of adenoacanthoma in the ovary always suggests the possibility of an association or precursor of endometriosis.

Great interest has developed in *atypical endometrial hyperplasia* in recent years, stimulated primarily by Hertig and his co-workers. In 1949 Hertig and Sommers reported a series of patients with adenocarcinoma of the endometrium who had had previous endometrial biopsies or curettages, in some instances many years previously. A study of the cases showed various atypicalities which were thought possibly to represent precursors of adenocarcinoma. They were described. From this and subsequent papers by Sturgis, by Gusberg, by Speert, and still later by TeLinde, certain ideas have evolved regarding atypical hyperplasia that may be prognostic importance. In the endometrium with atypical hyperplasia small areas may show the glands very closely packed together, practically back-to-back with little stroma between them, with hyperplasia of the lining cells, piling up of cells, and slight atypia. These areas are known as *adenomatous hyperplasia.* They have been found in prior biopsies and may represent a precancerous lesion.

Papillary infolding of glands, with piling up of the epithelium into the interior of the glands is another item of atypical hyperplasia. In still other forms, the glands may be very *variable in size and shape and formation*, with abnormal changes in some of the cells in these areas, with increase in size and shape of nuclei and with increased and abnormal mitoses. Finally, Hertig called attention to the description by Cullen in his book on Cancer of the Uterus in 1900, of areas of very pale-staining glands rather closely packed together but with otherwise normal appearing nuclei without particular piling-up of the cells or anaplasia. Cullen had stated that when these minute areas are found in the endometrium one should look closely for associated adenocarcinoma. Now, fifty years later, Hertig has pointed out that such pale staining areas of the endometrial glands may represent a precancerous lesion and may be present many years before the adenocarcinoma forms. Hertig has named this *carcinoma-in-situ of the endometrium.* While such interest has developed over these concepts of atypical endometrial hyperplasia, and the lesion called

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Fig. 134. Endometrial polyp with marked atypical hyperplasia simulating carcinoma. The glands are back to back with very little stroma between them, show marked piling up of cells two, three and four layers thick which have a somewhat pale appearance. The nuclei are irregular and there are rather numerous mitoses. This patient received estrogenic hormone continuously over a period of several years, and had bleeding which recurred although the hormone had been stopped. There were multiple polypi showing this pattern. Possibly this may represent early adenocarcinoma of the endometrium in polyps, but it seems more likely that it represents a marked change due to the estrogen, which may be reversible.

Fig. 135. Endometrial polyp showing marked hyperplasia and atypical changes apparently related to large doses of estrogenic hormone. The glands show marked piling up of epithelial cells with some dilatation on the right and a rather solid appearance of the gland cells on the left. Mitoses are frequent as are variations in size and shape of the nuclei. This might be considered a form of early adenocarcinoma, but since this patient had been receiving unusually large doses of estrogenic hormone, it was thought to be benign. No further treatment than curettage and removal of the polyp was followed by cure over the next fifteen years.

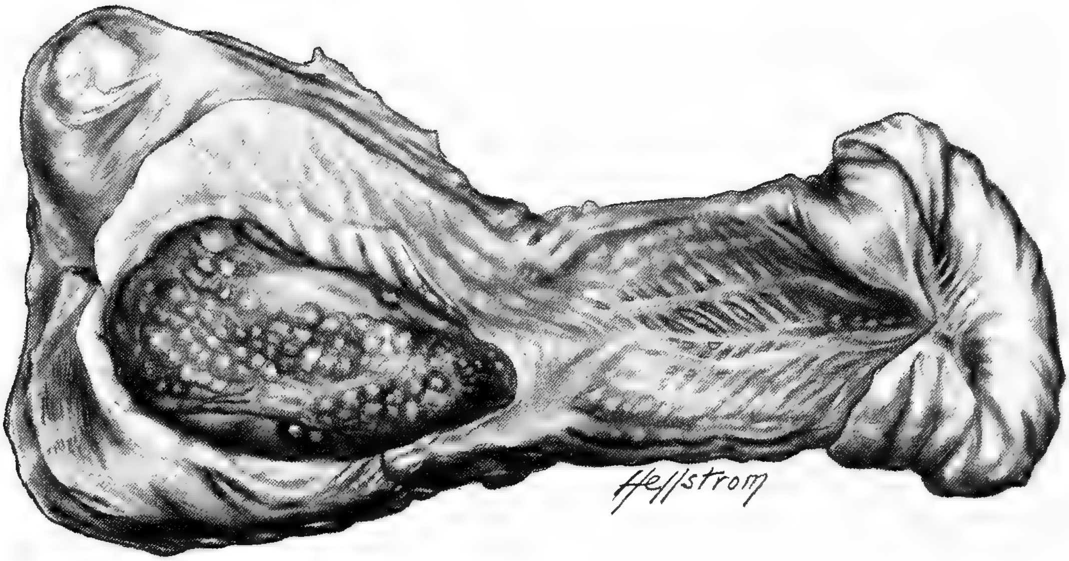

Fig. 136. Endometrial polyp. Benign, relatively large, in the small elongated uterus. from a patient with complete prolapse. No bleeding.

carcinoma-in-situ of the endometrium, and while many uteri are being removed for these diagnoses, and perhaps justifiably so, much more investigative work is necessary to put the final proof on these possible precancerous lesions.

The symptoms of adenocarcinoma of the endometrium include primarily postmenopausal spotting and bleeding in the majority of cases, and intermenstrual bleeding or less frequently menorrhagia in the premenopausal cases. Three-fourths of the cases are postmenopausal in occurrence. After the tumor has grown to some degree, ulceration develops from disturbance of its blood supply, or local infection, or inflammation, to cause the extrusion of small amounts of blood into the endometrial cavity and out the cervix and vagina. Of course the tumor has been growing for some time when bleeding has occurred

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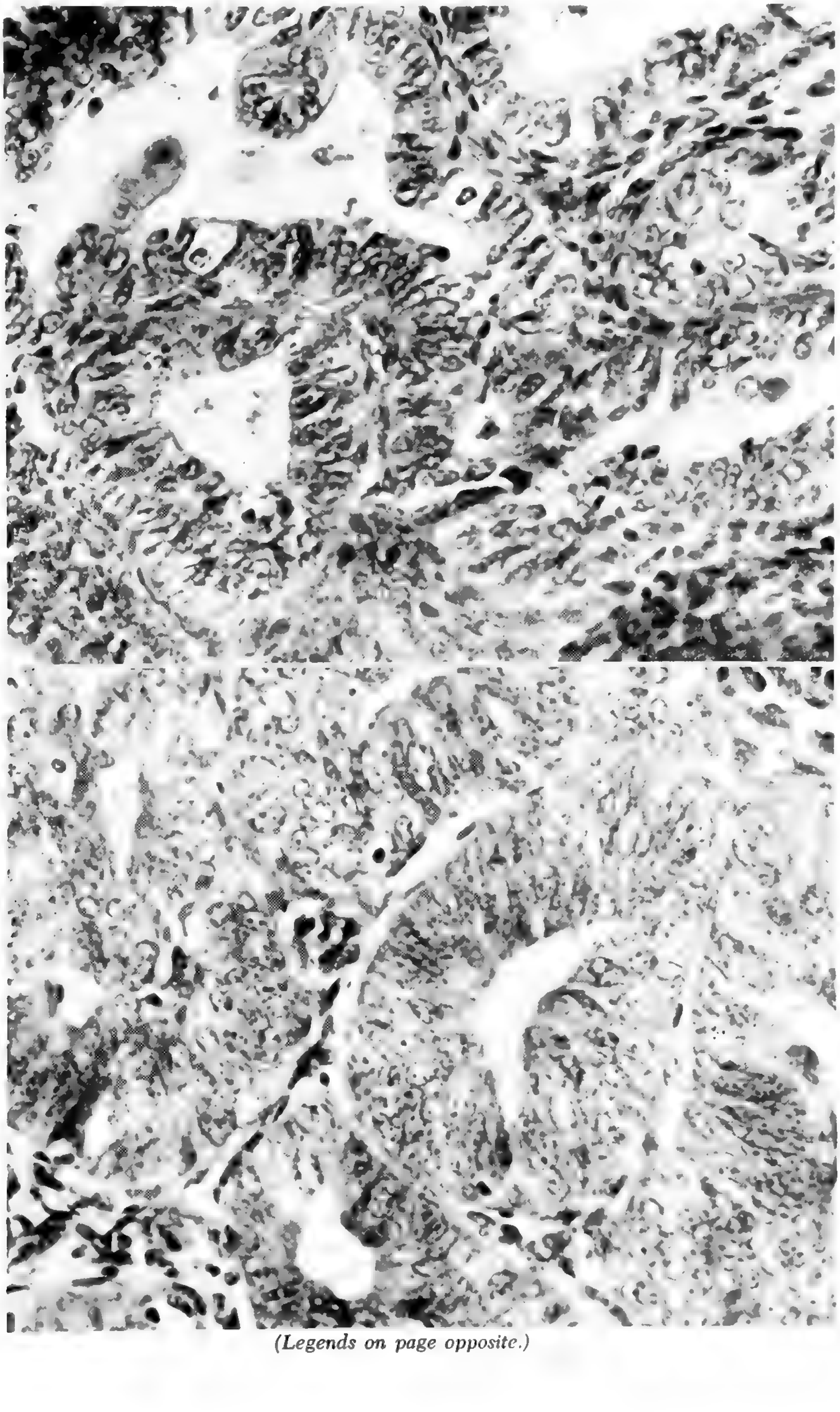
Fig. 137. Adenocarcinoma in an endometrial polyp. The glands are back to back. The cells are piled up to a remarkable degree, are pale staining with vesicular nuclei, although some of the nuclei showed marked atypical changes. This patient had had no estrogenic hormone. The polyp had appeared at the cervical os. After its excision and examination, hysterectomy was performed. The patient was cured. It is interpreted as adenocarcinoma, grade II.

Fig. 138. Adenocarcinoma of the endometrium. The glands are back to back, have extremely little stroma between them, are lined by two, three, or more layers of cells which are much larger and broader than normal and contain larger nuclei. Most of the nuclei are vesicular or vacuolated but there are also increased mitoses. This is a low grade adenocarcinoma (grade I).

and may have become quite advanced, metastasized, and become incurable. This is true of all malignancies in the body in which bleeding or symptoms from the cancer may be delayed until spread has already occurred through the body, preventing cure. In the twenty per cent of patients with adenocarcinoma of the endometrium who are pre-



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menopausal, most of those patients have intermenstrual bleeding, but some may have regular but prolonged menstruation, as menorrhagia without intermenstrual bleeding.

In a certain small percentage of cases the tumor is found when there has been no abnormal bleeding either before or after the menopause. In these instances the tumor is discovered accidentally after hysterectomy, or is found by the routine Papanicolaou cytology studies. The cytology studies are not dependable for great accuracy in determining adenocarcinoma of the endometrium, though approximately sixty per cent of cases may show a positive smear before any symptoms whatever have appeared. (This percentage may be an optimistic one.) These patients have no pain or other discomfort unless the tumor has extended beyond cure. The final diagnosis is made by examination of the curettings under the microscope. The indications for curettage are, of course, abnormal bleeding or positive Papanicolaou cytology studies. Any abnormal bleeding from the uterus is to be considered carcinoma until proved otherwise. This is invariably true in postmenopausal bleeding, although only thirty to fifty per cent of cases with this symptom will have

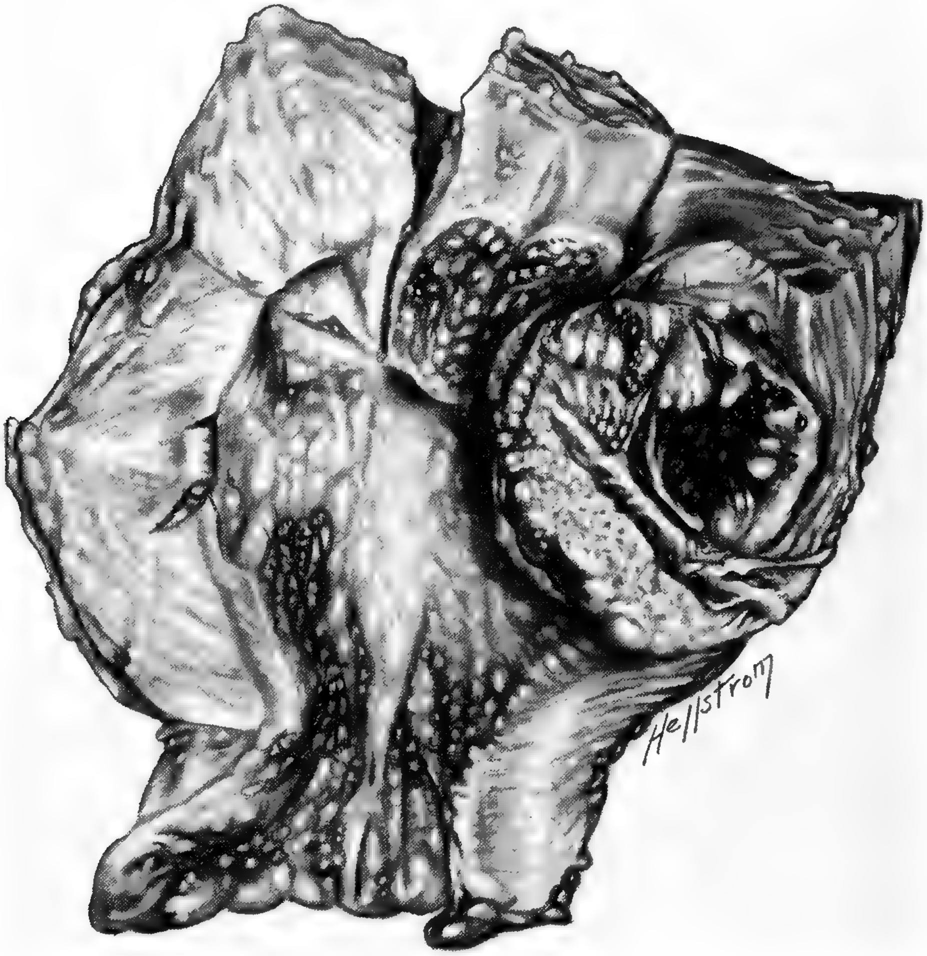


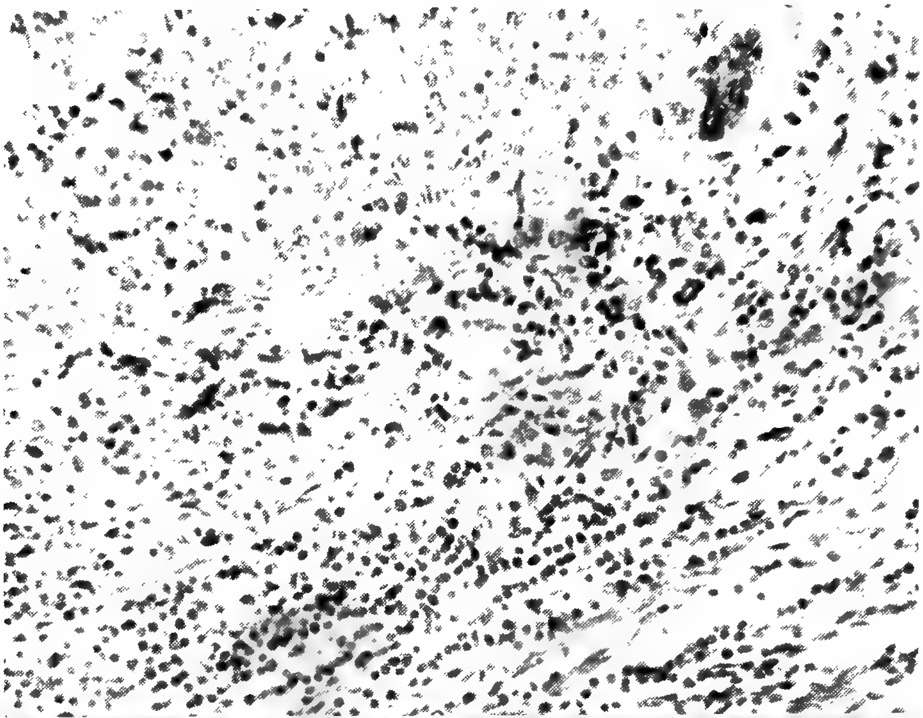
Fig. 139. Adenocarcinoma of endometrium, invading deeply into myometrium. Yellowish, granular, and partly necrotic. More often these cancers are papillary, tree-like, may be localized in one area or may involve the whole endometrium.

carcinoma. Irregular bleeding near the menopause and premenopausal intermenstrual bleeding also must be regarded as highly suspicious of malignancy until proved otherwise. Actually, young women with intermenstrual bleeding, when it seems associated so definitely with the time of ovulation, with the pain of Mittelschmerz and with negative Papanicolaou cytology study, may be observed carefully for a period of time. Also, intermenstrual bleeding that occurs during one single menstrual cycle may be observed, but if it recurs in the second cycle, curettage is indicated. Irregular bleeding in a single cycle most often has its relation to a defective follicle or defective corpus luteum, which does not maintain its hormone levels of secretion. If abnormal bleeding occurs in more than one cycle, in the absence of active inflammatory disease or pregnancy, curettage and biopsy of the cervix are indicated. Metrorrhagia, if prolonged more than one month, after the age of twenty-five, as a rule should have diagnostic curettage, both for diagnosis and for therapy: fortunately, the curettement is curative in more than half the patients.

In the performance of hysterectomy for other reasons than known carcinoma, many gynecologists advise that the patient should have curretage before hysterectomy is performed. A few have advised that curettage be performed one week before any hysterectomy in order that microscopic sections may be studied carefully to rule out malignancy. While this unquestionably is a valuable procedure, it does prolong hospitalization, has some increased risk, and certainly brings extra expense to the patient. Many others practice immediate curettage before hysterectomy, apparently depending on the gross appearance of the endometrium to distinguish carcinoma. This procedure is based on the strong feeling that all endometrial adenocarcinomas should have preoperative irradiation therapy. Many cannot agree with the necessity of that routine procedure and routine treatment. One must admit that endocervical squamous cell carcinoma, which may be suspected if the curette digs chunks of granular tissue from the endocervix, is far better treated with a different procedure than the ordinary conservative hysterectomy. Fortunately, this latter occurrence is an extraordinarily rare one, especially in the absence of any symptoms and in the absence of positive cytology, being encountered by the author only twice in over two-thousand hysterectomies. Each of these particular cases had postoperative irradiation therapy and had no recurrence after five years. Still this is not the proper treatment for carcinoma of the cervix.

The difficulties in routine preoperative curettage for unsuspected adenocarcinoma of the endometrium include first that of incomplete sampling of the endometrial cavity, especially if there are myomas of the uterus which enlarge and distort the cavity, and secondly the inconclusiveness of the gross interpretation of endometrium as to the presence of adenocarcinoma. In well-formed carcinomas or advanced cases the granular, greyish, friable tissue is obviously malignant, but in a surprising degree of less extensive malignancies, no one can determine by the gross appearance of endometrium that carcinoma is present. Of course, in the patient *where one suspects the possibility of endometrial carcinoma or carcinoma of the cervix, one should always perform curettage and biopsy* before more definitive therapy. But without a clinical suspicion of such malignancy and with negative cytology, routine diagnostic curettage is not completely accepted because of the impossibilities of accurate gross diagnosis, because of the possibility of stirring up a tumor and spreading cells, particularly having them drawn down in the vagina, and because frozen section of the endometrium is an impractical procedure by the majority of pathologists in this country today. Undoubtedly there are a few pathologists and technicians who are capable of performing accurate frozen section diagnosis of endometrium from

Fig. 140. Pale staining malignant tumor cells with many mitoses press deeply into the myometrium. This represents a grade IV adenocarcinoma, with little glandular form. Deeper in the myometrium are numerous lymphocytes and plasma cells, caused by infection in the tumor. Patient died in one year with metastases to the lungs.



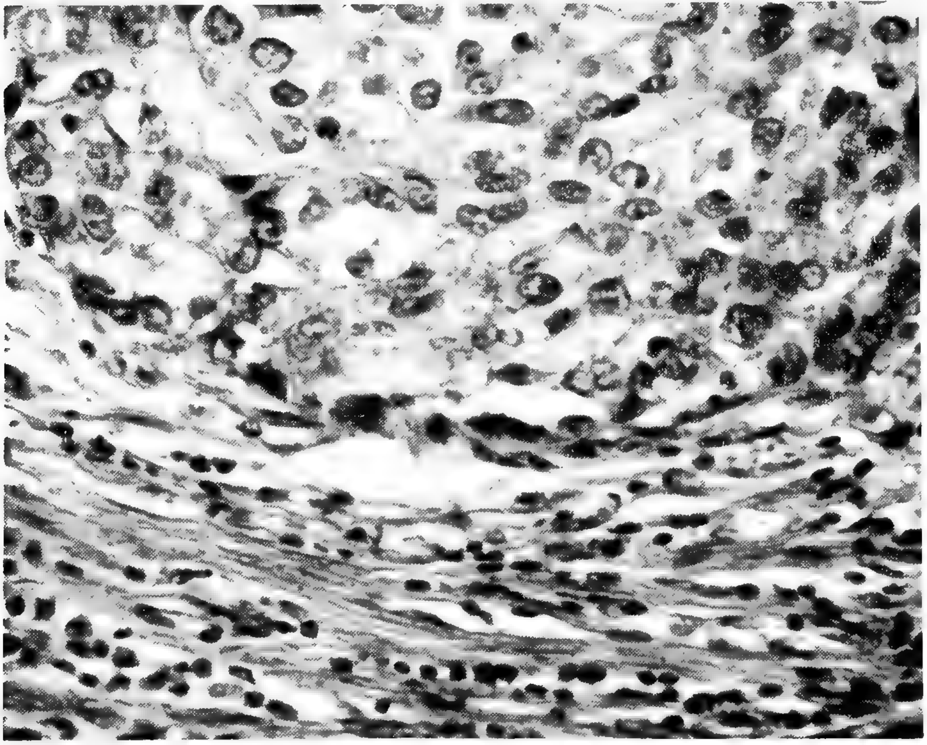


Fig. 141. Endometrial carcinoma, grade IV, invading the wall of the uterus. The solid portion of the malignant cells in the upper portion of the photograph is preceded by a moderate inflammatory reaction in the myometrium.

curettings. Every excised uterus should be opened carefully and inspected by the operating surgeon at the time of excision. If there is gross adenocarcinoma present, and one can determine this better in the whole specimen than in the curettings, immediately the tubes and ovaries should be excised.

The treatment of adenocarcinoma of the endometrium is primarily total hysterectomy and bilateral salpingo-oophorectomy. Preoperative irradiation therapy has become increasingly popular in this country since being introduced by Healey in 1936 from the Memorial Hospital. He advised that 3,000 to 4,000 mgm. hours of radium be applied to the endometrial cavity, being distributed as well as possible, to be followed six weeks later by the operative procedure of total hysterectomy and bilateral salpingo-oophorectomy. The radium has been inserted in a tandem in line in a single rubber tube into the uterine cavity, but since that did not give a good distribution and produced hot points in some areas and insufficient radiation in the fornices and sides of the uterus, various other methods have been used to insert the radium. This includes the use of packing containing radium plaques which is placed in the uterus (Heyman). Others have introduced Y-shaped applicators to extend the radium into each cornu of the uterus (Schmitz). The hysterostat designed by Friedman, an ingenious method of arranging the radium in a triangular manner in the uterus, has given a good distribution. More recently Hendricks has suggested the use of a string of beads containing radium which are packed into the uterus. It would seem that these possibly might become tangled and difficult to remove. Still others (Miller) have advised the use of external irradiation without intra-uterine radium. Thinking that sufficient intra-uterine radium if distributed properly, might completely destroy adenocarcinoma of the endometrium, unusually large doses were given by Gray, Friedman and Randall, using the Friedman hysterostat. Surprisingly, after these very large doses of radium, varying from 8,000 to 12,000 mgm. hours, residual carcinoma was found in the majority of that small series. The doses of radium in these particular cases were so high as to cause delayed healing and other complications. It is obvious that radium therapy, while it may destroy the carcinoma in a certain percentage of cases, cannot be depended upon alone to be curative of this particular lesion.

The majority of gynecologists in the country feel that preoperative radium is of great value in the final cure rates. Theoretically, the radium may paralyze or stun the malignant cells, seal off the lymphatics about the

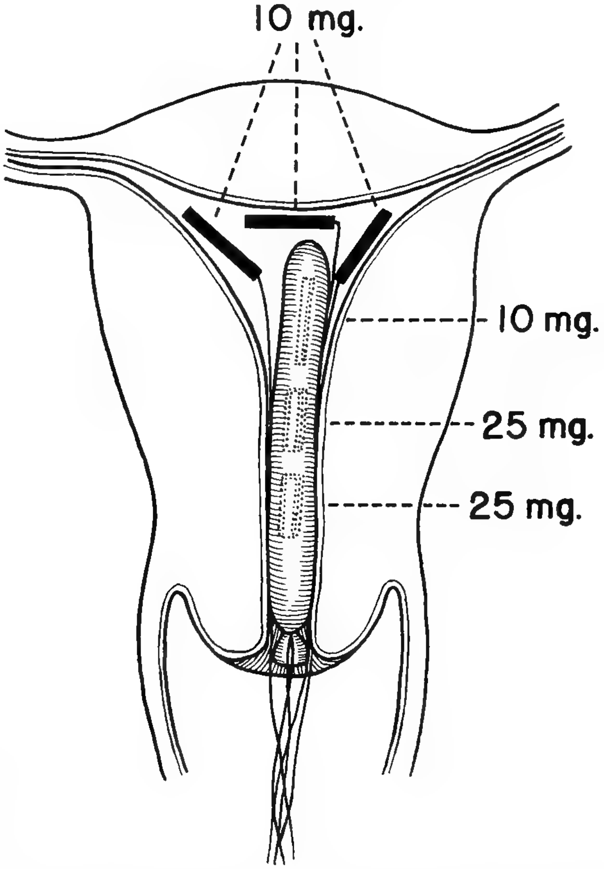


Fig. 142. Insertion of radium in uterus for adenocarcinoma of endometrium. The straight tandem alone does not irradiate the fornices of the endometrial cavity. The placement of the radium tubes is checked by x-ray films. Many other methods of placing the radium is preferred by different individuals. Total hysterectomy and bilateral salpingo-oophorectomy are performed from three days to six weeks later.

uterus, obliterate many of the blood vessels, reduce the size of the uterus greatly and make the operative procedure more accurate, and finally eradicate infection from within the uterus (which is doubtful). The adherents of this form of combined treatment have pointed out that the percentage of cures has increased from fifty-five or sixty-five percent to seventy, eighty, or even ninety percent. The larger series of surgery alone with the lower percentage of cure are from older statistics, whereas the newer statistics in the past twenty years are really insufficient for quite the same comparison for the final assessment of this treatment.

The great improvement in cure rate in the past twenty years may be due in part to earlier diagnosis. An examination of the case records of a large number of patients treated in the Louisville General Hospital before twenty years ago showed the majority of the cases were of such extensive involvement that no method of cure could be expected to be successful, whereas at the present time the majority of cases are relatively early; certainly this is true among private patients. With the education of the patient and the physician, and the availability of diagnostic procedures, including cytology and curettage, it is obvious that the earlier cases of today are not comparable with those of twenty years ago. Recently a few observers have pressed again for surgery alone without preoperative radiation in the treatment of this disease. This has been suggested particularly by McKelvey and his group, and by McLennan and his group.

It does seem that the patient with relatively advanced growth, with enlargement of the uterus, with relatively long-continued bleeding, with the finding of a large amount of carcinomatous tissue on exploration of the uterus may be aided by preoperative radium therapy, particularly to shrink the uterus and close many of the lymphatics and blood vessels. Perhaps it does stun the cells that might be spread by the operative procedure. On the other hand, in the relatively early case with a short history of bleeding, with a small amount of tumor, with a uterus of normal size, probably either the combined treatment or surgery alone will give about the same results.

Regardless of the best treatment, as regards combined irradiation and surgery or surgery alone, there remains a loss of ten, twenty, or thirty per cent of patients. In some of these this is undoubtedly due to extension of the tumor and distant metastasis before the patient is treated, beyond any possible cure, with our known methods of treatment. On the other hand, some of them might be cured by the more radical operative procedures, as the Wertheim operation with excision of pelvic lymph nodes.

In some sixteen per cent of cases metastases are found in lymph nodes at the time of operation, if such lymph nodes are excised and studied (Randall). Obviously, these cases are not cured by simple total hysterectomy and bilateral salpingo-oophorectomy, and they are not cured by irradiation therapy as a rule, because the tumor dose required to destroy adenocarcinoma is an extremely large one (more than that of the epidermoid carcinomas of the cervix), and only excision of the pelvic lymph nodes and a wider excision of the pelvic organs could possibly cure these patients. Unfortunately, many of the patients are elderly, obese, have medical complications, and are simply not good candidates for such radical surgery. In those patients who are relatively young, who are not overweight, who do not have medical complications, it would seem that the more radical operation with pelvic node dissection is the better procedure. That fact that there is a relatively high cure rate as compared with other forms of carcinoma in the pelvic organs tends to make the physician complacent in the treatment of this disease and to use the more conservative surgical approach in order to avoid postoperative and late complications. The great effort required by the surgeon and the more prolonged convalescence are deterents to this extensive operative procedure. It is a great temptation to treat the patient with more conservative total hysterectomy and bilateral salpingo-oophorectomy because the convalescence is much more rapid and the complications much less frequent. As with every disease and situation in medicine, each case must be individualized. In many patients, a relatively conservative approach is necessary because of their general condition.

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CHAPTER VII

Diseases of the Myometrium

MYOMAS OF THE UTERUS

Because of the frequency of occurrence, myoma of the uterus is one of the most important lesions in gynecology. Other terms used for this tumor are fibromyoma, leiomyoma, leiofibromyoma, and "fibroid." These various names indicate that the tumor is composed of both smooth muscle tissue and fibrous tissue. The more commonly used term is myoma of the uterus, or when more than one are present, myomas of the uterus, or myomata uteri. It is a rare occasion when only a single tumor is present. The other and even more popularly used term is "fibroid" of the uterus, or "fibroid tumor."

Myoma of the uterus is an encapsulated benign tumor, composed of both smooth muscle and connective tissue. Usually, approximately two-thirds of the tumor is composed of smooth muscle, and one-third of connective tissue. This proportion may vary greatly. In some of the tumors, most of the tissue is fibrous tissue, in others a larger percentage of smooth muscle is present. The tumor of itself is invariably benign, although a malignant change may occur, known as sarcoma of the uterus. Sarcoma is a malignant neoplasm of connective tissue, and this term used here suggests that the connective tissue portion of the tumor is the origin of the malignant form when it occurs. Another term for the malignant change is leiomyosarcoma, which suggests that not only the connective tissue portion, but also the smooth muscle, may develop malignant characteristics. Certainly in perusing these tumors it would appear that the smooth muscle cell has become malignant.

Myomas are discovered clinically in greatest frequency between the ages of thirty-five and forty-five years. That is, the patient develops symptoms related to the myomas more frequently in the mature sexual age. In a smaller percentage these tumors are found between the ages of twenty and thirty years, on occasion the tumors developing to quite some size in the early twenties. Very rarely they are found at ages of sixteen or eighteen, but never before menstruation has begun.

Near the menopause myomas of the uterus are found frequently, often associated with abnormal bleeding, though not necessarily the cause. After the menopause, myomas of the uterus also are found in great numbers, but they tend to shrink and less often cause any symptoms. If the myomas grow and enlarge after the menopause, one always suspects a malignant change, as sarcoma in the myoma, though this may not be the case and the enlarging tumor may be entirely benign. It is said that twenty-five or thirty per cent of all women develop myomas of the uterus. This must be true from experience with the clinical examination of women, as these "knobs" on the uterus are palpated very frequently. If a large series of uteri obtained at the time of the menopause were sliced thinly and examined most carefully, perhaps small myomas would be found in one hundred per cent of cases; certainly, the percentage would be very large. In Negro women the myomas of the uterus seem much more frequent in occurrence, and to grow more rapidly and much larger. This is noted particularly in the teaching clinics over the country. The increased incidence evidently is a racial characteristic.

Myomas of the uterus develop in their

smallest form as a proliferation of the fibromuscular tissue around extremely small blood vessels (Otto Schwartz, and others). The cause of the origin of the tumors is unknown, but the growth is related largely to estrogenic hormone, because the myoma does not develop and grow in the absence of this hormone. This explains the absence of these tumors before the hormone secretions of puberty and after bilateral oophorectomy. New ones do not appear after the menopause, and those already present cease to grow, and may become smaller. (One would think this tumor might conceivably develop after the

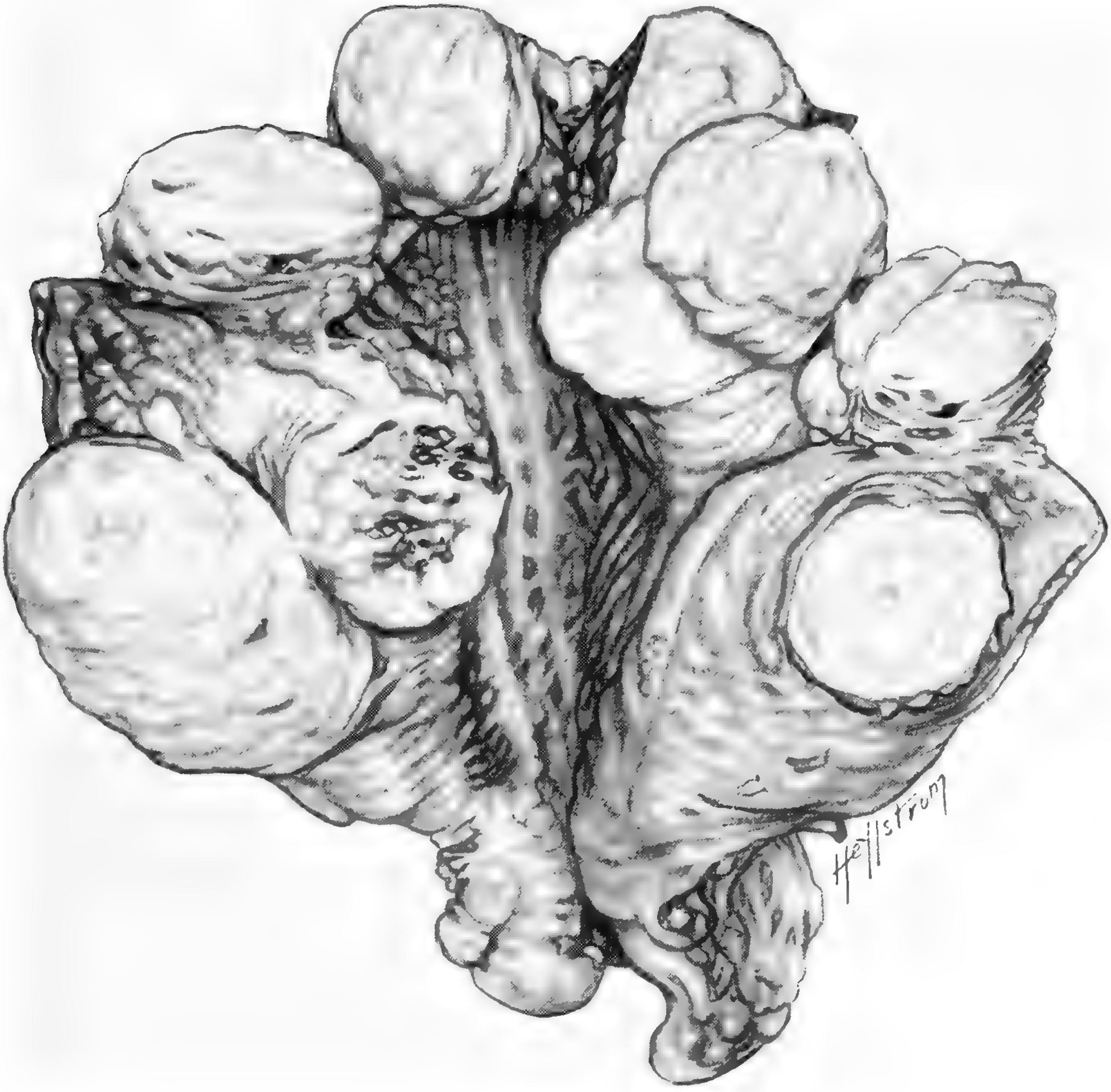

Fig. 143. Myomata uteri, submucous, intramural, and subserous. Menometrorrhagia was produced by the submucous tumors, one showing areas of hemorrhage. Endometrial hyperplasia and polyps are benign, indicate a strong estrogenic stimulus.

menopause, because estrogen secretions from the adrenal gland do continue in some individuals.) Some years ago, Lipschutz performed some interesting experiments, producing myomas along the esophagus and gastrointestinal tract of guinea pigs by administering estrogen alone. The addition of progesterone to the estrogen prevented the formation of the tumors, and progesterone caused some regression after they had formed. However, in those experiments fibromyomas were not produced in the uterus, which means that this experiment evidently is not applicable to the woman. While estrogens are most important in the growth of myomas of the uterus, it would appear that some other factor than estrogen alone is necessary as an original stimulus for the formation of this usually benign growth.

Myomas of the uterus are classified particularly according to their location in regard to the uterus. The most frequently occurring tumors are of *intramural* and *subserous* types, the encapsulated tumors occurring well within the wall of the uterus, causing perhaps great enlargement and distortion from the multiple nodules (the single nodule is rather uncommon). They may bulge up beneath the serosa, gradually enlarging up into the abdominal cavity to great size. The *submucous* myoma may press well into the interior of the uterus and cause much distortion of the endometrial cavity, as a single tumor or multiple nodules. The *submucous pedunculated* tumor may develop from the squeezing and contraction of the uterine muscles, which attempt to expel the foreign body protruding into the cavity. The tumor may be expressed into the dilated cervix, or completely through the cervix and into the vagina, when there may have developed a relatively small pedicle. The tumors, when expressed, vary from three to eight or ten centimeters in diameter. Subserous pedunculated tumors are rather

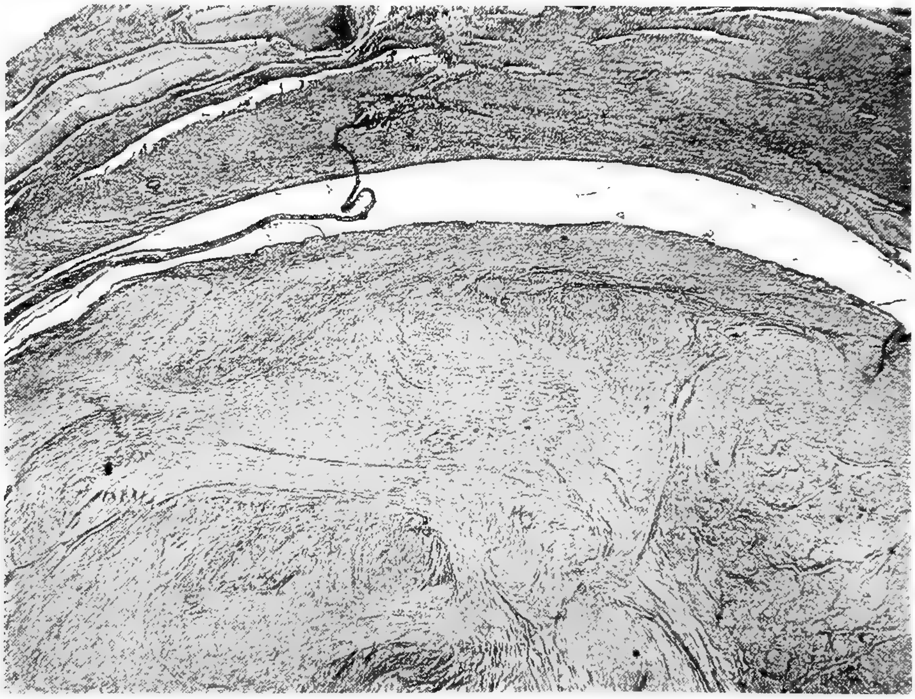

Fig. 144. Myoma of uterus, low power. The upper portion of the photograph shows the interlacing bundles of muscle and connective tissue which has a sharp demarcation from the normal, though compressed, muscularis of the myometrium. The separation of the myoma from the myometrium is due to shrinkage in the fixation of the material.

frequently found, the tumor beginning as a subserous nodule, and growing outward into the abdominal cavity. Quite large tumors may have a pedicle one to three or four centimeters thick, which contain the arteries and veins that supply the tumor. As these tumors become quite large, especially if their original pedicle is rather small, they may develop small areas of ischemia with slight necrosis, so that they become "sticky," and adjacent omentum, bowel and parietal peritoneum become adherent to the tumor. The blood vessels of these adherent areas become anastamotic with these in the myoma and may produce a greater blood supply to the tumor, evidently being stimulated to do so by the need for nourishment. Such pedunculated parasitic myomas may weigh fifteen or twenty pounds, or much more, and may obtain most of their blood supply from the blood vessels of adjacent organs. Sometimes the tumor becomes completely parasitic and completely separated from the uterus, and it may become a *migratory* tumor, being found in the upper abdomen and some distance from the uterus. *Intraligamentary* myomas are similar to the subserous tumors, growing from the outer part of the uterine wall, and by their position extend between the leaves of the broad ligament, approaching the wall of the pelvis. As a myoma enlarges, it may press the normal-sized corpus of the uterus far to the opposite side of the pelvis, or up out of the pelvis into the abdomen. Intraligamentary tumors may be present on both sides in the same patient, and may cause great distortion of the blood vessels and remarkable displacement of the ureters, adding to the technical difficulties in the removal of these tumors.

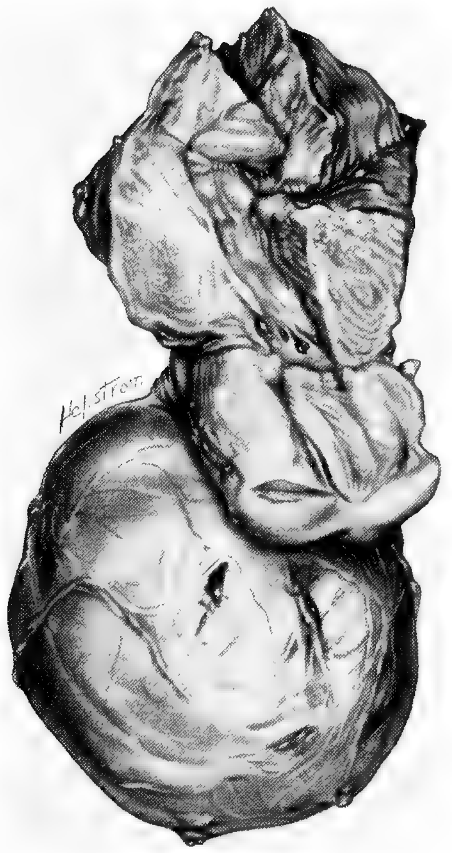

Fig. 145. Myoma of lower uterine segment or cervix, buried completely beneath the cul-de-sac peritoneum and placed between the vagina and rectum. Seedling myomas were found scattered through the myometrium of the corpus.

Various changes may occur in myomas, and these are called forms of degeneration. One wonders if these changes really should be named degeneration. They include *hyaline degeneration, hemorrhage into a* myoma, *carneous degeneration, cystic degeneration, calcifying degeneration, fatty degeneration,* and *malignant degeneration.*

The hyaline degeneration is the most frequent change found in the myoma. In various areas of the tumor, the muscle and connective tissue cells melt into a hyaline material, in minute or extensive portions. This change seems due to interference with or insufficient blood supply to the tumor. Apparently all of the tumor cells may not receive all of the nourishment and oxygen necessary for their individual existence. There are no symptoms associated with hyaline degeneration of a myoma, that have been elucidated. Hemorrhage into a myoma may occur in a small percentage of these tumors, perhaps as a form of apoplexy, due to some weakness in a blood vessel of unknown etiology. Conceivably, the rupture of a blood vessel within a tumor might be related to trauma; as a rule, no history of injury is obtained. Hemorrhage into a tumor may produce essentially no symptoms, but on occasion may cause severe low abdominal pain, and the tumor may seem to enlarge to a slight or moderate degree. Because of this sudden and marked pain, one may suspect the onset of pelvic inflammatory disease, or possibly even a tumor or cyst with twisted pedicle. The true nature may be clarified only after the excised uterus is opened and the hemorrhage is seen. More often, the alert clinician may suspect hemorrhage within a myoma, because of sudden abdominal pain, and yet the excised specimen may show none.

Carneous degeneration, a reddish, meaty appearance of the myoma, may be caused by the absorption of blood pigment through the myoma from preceding hemorrhage. The exact cause of carneous degeneration is not clear. A tumor with this appearance, especially if quite "meaty" and finely granular, must be carefully distinguished from sarcoma of the uterus. In fact, one often suspects that sarcoma is present, and the diagnosis is clarified only by the microscopic sections.

Cystic degeneration occurs as the tumor becomes large, in some when only moderately large; most of the extremely large tumors that have been reported have formed cysts in the interior. These liquefying areas have

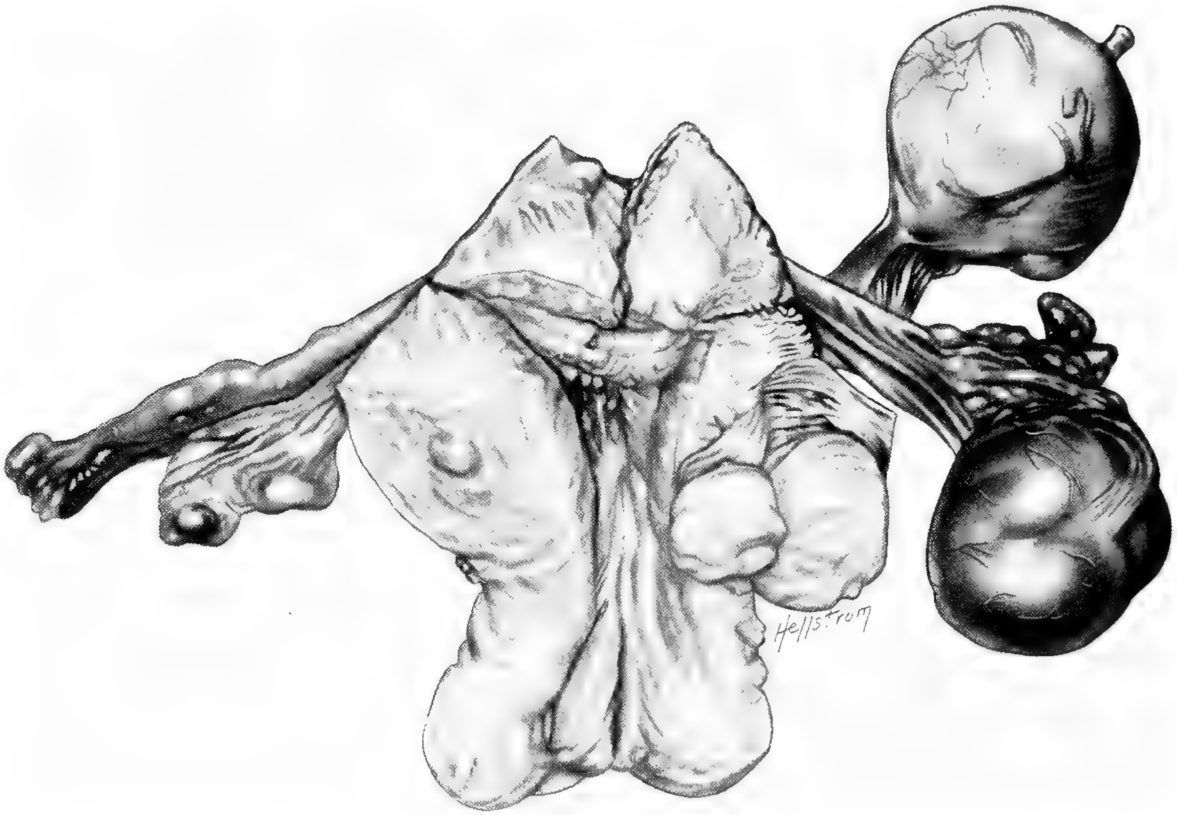

Fig. 146. Myoma of right round ligament. In addition there are small intramural and subserous myomas. The endometrium shows polypoid endometrial hyperplasia. The right ovary contains a dermoid cyst, of yellowish color. This patient had pelvic pain and menorrhagia, was near the menopause.

no epithelial lining and represent a change apparently due to interference with blood supply, an inability of the uterus to extend sufficient blood into the tumor to supply all of its cells with sufficient nutrition. The Army Medical Museum contains a one hundred and nine pound specimen removed by Cullen. The myoma had changed almost entirely into a cyst. Cullen said that he used four assistants who held a wash tub covered with sterile sheets, into which the large tumor was rolled, from a four foot incision. After the operation the patient weighed ninety-three pounds. She made a good recovery.

Calcification in a myoma, known as calcifying degeneration, again seems related to imperfect blood supply to the tumor, though this must not be the entire explanation. Calcification occurs more frequently after the menopause, when ordinarily there is moderate or marked shrinkage of the tumor. This calcification, of itself, is not important, if there are not other pelvic abnormalities. The presence of calcification may be suspected when a tumor feels extremely hard and irregular, but is proved clinically only by the x-ray film of the pelvis. Often the calcified tumor is found incidentally when x-ray films are taken for other diagnostic purposes.

Fatty degeneration occurs in a small percentage of myomas, and presents a golden yellow appearance, usually in only small areas, but sometimes homogeneously throughout the tumor. A few instances of lipomas of the uterus have been recorded (Hall), and evidently such a true benign neoplasm may occur, but more often a fatty encapsulated tumor must represent fatty degeneration of a myoma. There is no clinical significance of the lipoid change itself.

Malignant change in a myoma, malignant degeneration, sarcomatous degeneration, or secondary sarcoma (primary sarcoma meaning that arising in the muscle wall itself

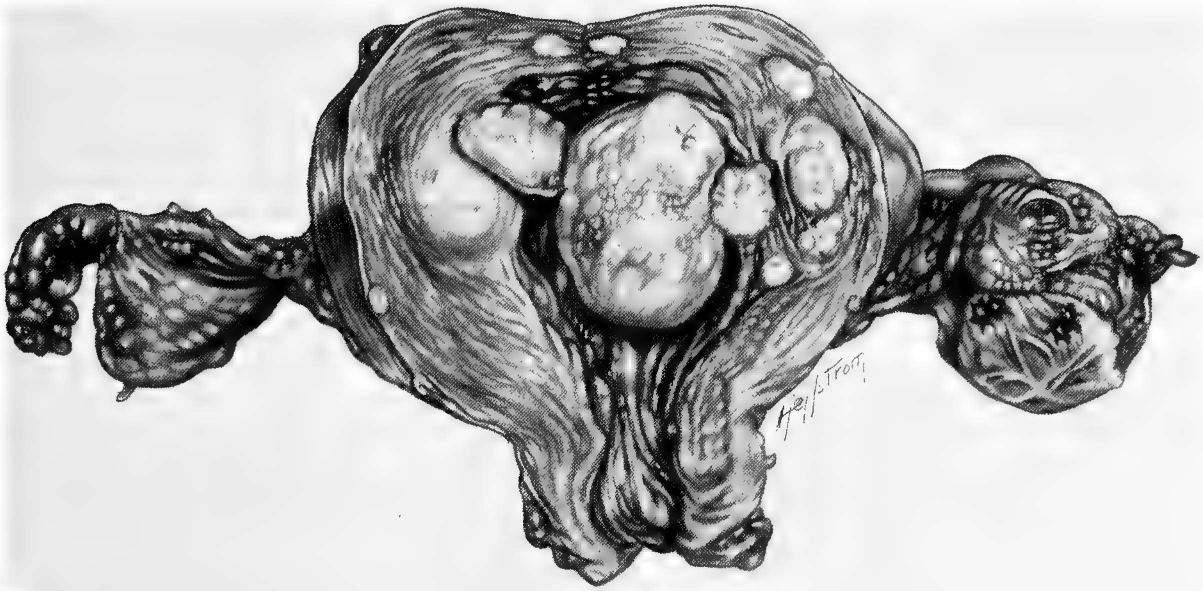

Fig. 147. Submucous myomas here have caused marked menorrhagia and anemia. Both ovaries were adherent with endometrial implants; the right contained a small endometrial cyst.

without a previous myoma) is said to occur in one in two hundred patients who have myomas. This change, again called degeneration, is hardly degeneration in the sense of necrosis, liquefication and calcification, with inert cells, because this has become a very vigorous tumor indeed. However, the term, malignant degeneration, has been used for so many years with respect to malignant change and must connote the change from pleasant orderly cells into abnormal invasive cells of "degenerate" character. Sarcoma of the uterus will be discussed later in this section.

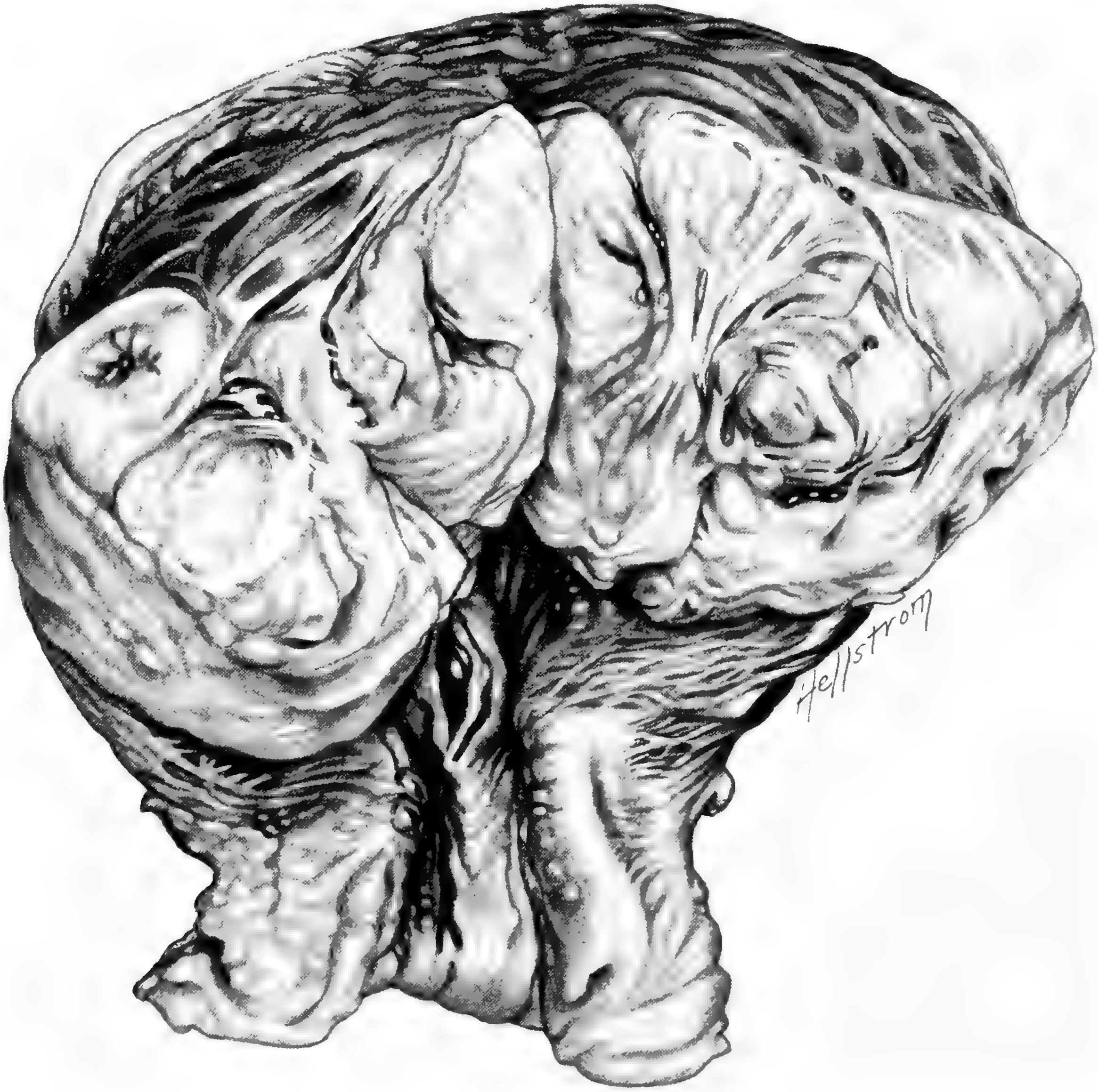

Fig. 148. Sarcoma in myoma. Incidental and unexpected finding. Fortunately cured after eight years. Tubes and ovaries were not removed, because condition at operation was thought benign.

EFFECT OF PREGNANCY ON MYOMAS

The effect of pregnancy on myomas of the uterus has been noted with interest for a very long time. After a pregnancy has occurred myomas, discovered before pregnancy, appear to grow and enlarge to considerable degree in the majority of the cases. This enlargement is due to the hormones of pregnancy. Frequently the myomas increase half again in size or double or triple their size in the first few months of pregnancy. But during this time the uterus is showing such great enlargement, that sometimes it is difficult to discern and separate the tumor itself, or it may become more prominent and obvious as the uterus softens from the effects of pregnancy. In recent years, papers have appeared to suggest that multiplication of the cells is not a prominent factor in the pregnancy changes of the myomas, but that the smooth muscle cells become enlarged during pregnancy, perhaps twice their normal size, to cause enlargement of the myomas. On the other hand, some myomas evidently do not enlarge during pregnancy. After a pregnancy has been completed by Caesarian section, the tumor often does not seem nearly so large as during the pregnancy. Certainly after involution of the uterus, the tumors show relatively little increase in size over the pre-pregnancy state. The rate of growth of myomas of the uterus is very variable, being rather rapid over a few months in some instances, regardless of pregnancy, or growing very slowly or showing no change at all over prolonged intervals in other instances.

In general, myomas are not operated on during pregnancy, unless there is doubt of the true diagnosis, the inlet is obstructed, much pelvic pain has occurred, or a quite mobile pedunculated tumor is present which might be twisted. The general opinion is that necessary pelvic surgery should be delayed until after the twelfth week of pregnancy to avoid incidental abortion, but some have doubted the necessity of this delay. If a threatened abortion is present before an operation is performed, most often it becomes inevitable after any surgical procedure. If the uterus is quiescent, extensive surgical procedures may be performed without disturbance of the pregnancy, if great care and gentleness are exercised.

SYMPTOMS OF MYOMAS

Symptoms of myomas of the uterus may be absent, or may include abnormal bleeding, pelvic pain, and an obvious pelvic tumor mass. In the majority of cases small myomas are associated with no symptoms, no pain, no abnormal bleeding, and no interference with pelvic function. The small tumors may vary from a few millimeters in diameter (seedlings) up to three or four centimeters in diameter. The small tumors, without symptoms, never require treatment of themselves, but should be observed by pelvic examination at six month intervals.

Abnormal bleeding, as metrorrhagia or menorrhagia, is frequently associated with myomas of the uterus. Until recent years, the bleeding was thought caused by the myomas themselves, but now the intramural and subserous tumors are thought not to cause abnormal bleeding. The tumors are associated with meno-metrorrhagia in a greater percentage of cases than is the normal uterus, but the bleeding is thought due to endocrine dysfunction, a hormonal imbalance which may have some relation to the very presence of the myomas. Further work is necessary to clarify this relation to abnormal bleeding. On the other hand, the submucous myoma is thought to be a definite cause of menorrhagia, although in some instance menstruation is quite normal. The submucous myoma may cause severe menorrhagia, enough to produce a marked secondary anemia.

Pelvic pain may be caused by myomas of

the uterus, if the tumors are sufficiently large to press against the side walls of the pelvis and involve the lateral nerve trunks and major blood vessels. Growth forward against the bladder often causes urinary frequency and a sense of pressure, and occasionally may cause retention of urine. Growth of the tumor toward the rectum may cause rectal discomfort, hemorrhoid formation, and rarely constipation. More often constipation is not relieved by the removal of a fibroid tumor. When pelvic pain of varying degree and variable location is associated with small myomas of the uterus, it must be suspected that the tumors may not be the cause of the symptom, as removal of the tumors by hysterectomy in such a case often does not cure the patient's complaints. Unless there is associated adnexal pathology, urinary tract disease, or bowel disease, as diverticulitis, then it is quite possible that the pain is of functional origin.

Pelvic pain, in the form of severe dysmenorrhea, may be related to myomas of the uterus. While more often the menstrual pain is not severe, in some instances, it may be incapacitating. When pelvic pain associated with myomas is of the intermenstrual type, the tumors must be of some size. When occurring only with menstruation, the tumors may be relatively small. Also, myomas may be associated with dyspareunia, in some instances sexual intercourse causing much discomfort if the tumors are displaced low in the pelvis and in the cul-de-sac. The normal elasticity of the vagina may be restricted, and the tumor masses may prove to be quite tender. As mentioned earlier, marked pelvic pain may be associated with hemorrhage into a myoma. Another form of severe pain is caused by torsion of a pedicle of a pedunculated myoma; this is one of the emergencies in pelvic surgery. When this does occur, the abdomen becomes rigid, the tumor mass extraordinarily tender, and operation is indicated rather clearly.

The patient may complain of a tumor mass which she has observed, first as a small growth in the lower abdomen, which has enlarged slowly over a period of years to fill the entire abdomen. These masses may cause varying degrees of discomfort, a crowded pressure sensation, and a feeling of heaviness, weight or distention. On some occasions a very large tumor mass produces no symptoms whatever, and the patient may be surprised to learn she has a large tumor.

Sometimes the patient's only complaint is sterility. Small myomas are found in many patients who have sterility, probably because of the frequency of both of these conditions, particularly the myoma. Those tumors, from one to three or four centimeters in diameter, are considered no deterrent to fertility of themselves, and require no treatment as a rule. On the other hand, the occasional sizeable myoma with a diameter of six or eight centimeters, or multiple tumors causing marked distortion of the uterus, may be treated by myomectomy. Pregnancy may follow in a certain percentage of cases. Apparently there is a causal relationship to the sterility in selected cases.

DIAGNOSIS OF MYOMAS

The diagnosis of myomas of the uterus is made by bimanual examination, the enlargement, irregularities and nodules being readily determined. If the tumor mass extends to one side and is not very moveable, one may suspect accompanying pelvic inflammatory disease or an intraligamentary tumor. If the mass is separate from the body of the uterus, one may suspect a pedunculated myoma or an ovarian tumor. This latter differentiation is most important, because the myoma may be observed, but an ovarian tumor should be excised in the immediate future. This differentiation may be impossible without exploration. Some may use examination under anesthesia or culdoscopy, in which the cystoscope-like instrument is inserted into the cul-de-sac in the knee chest position.

If the tumor is found after the menopause and recent symptoms or observation suggests active growth, a sarcoma in a myoma is suspected, and immediate surgery is indicated.

If the uterus is rather symmetrical, perhaps somewhat soft, with slight bluish congestion of the vagina and cervix, and slight breast changes, one would suspect pregnancy, with or without a missed menstrual period. Myomas may be present coincidentally, or the irregular enlargement may be due entirely to a normal pregnancy. Pregnancy tests or observation, and x-ray films when larger than a pregnancy of four and one-half months duration, must be considered in all cases where there is any reasonable doubt of pregnancy. It is always so much more comforting to have the results of these tests or to have had a period of observation when the abdomen is opened and a rather symmetrical, slightly soft bluish uterus is encountered. Occasionally one suspects pregnancy, but the tests are negative (after three months, the titre of chorionic gonadatrophin falls to a low level and may not stimulate the experimental animal's gonads). In such an instance, observation may prove the accuracy of a clinical impression of possible pregnancy, and every clinician must maintain a keen awareness of this possibility.

An example of the difficulties in diagnosis was brought home to the author by Cullen, who operated on a young woman, daughter of a socially prominent family, and student in a famous college for women in the East. When the abdomen was opened Cullen found the uterus symmetrical, somewhat soft and bluish. Although he felt there probably was no pregnancy because of his knowledge of the patient, he closed the abdomen. When subsequent pregnancy tests were negative and observation for six weeks showed an evident tumor, the abdomen was re-opened and a necessary hysterectomy performed. This was traumatic to the patient and family, but occasionally such a dilemma must be solved by that routine. Errors have been made and will continue to be made in the excision of uteri containing normal pregnancies. With care and alert observation the error will occur infrequently.

The diagnosis of myomas in a symmetrically enlarged uterus may be difficult, but it is not too material as to whether the patient has adenomyosis, subinvolution, fibrosis or myoma, if the symptoms are positive and disabling. With menorrhagia or dysmenorrhea, either adenomyosis or submucous myoma may be present. With the use of a uterine sound or the curette during curettage, the submucous myoma may be palpated (but it may be missed too). Hysterogram may show the irregularity in the endometrial cavity. Preoperative diagnosis is important if one wishes to perform myomectomy of such a tumor, but most often preservation of the uterus seems unnecessary because the patient may be forty years of age or older and may have completed her family. A real exception is sterility. Perhaps more abdominal submucous myomectomies may be performed, as more patients are seen where a desire for pregnancy is a real reason to save the uterus.

TREATMENT OF MYOMAS

The treatment of myomas of the uterus has been quite variable from one situation to another, and from one individual physician to another. In many instances, the mere finding of small myomas of the uterus has been used as an excuse for immediate hysterectomy. Often the patient has been pressed for a rapid arrangement for surgical operation. This has been a part of the basis for the criticism of the wide use of hysterectomy. Small myomas of the uterus, without other findings or serious symptoms, always should have observation, unless there is severe and incapacitating dysmenorrhea, observed over a period of time, or severe menorrhagia suggesting a submucous myoma, which may be studied further with the uterine probe or hysterogram, or unless there are other and obvious symptoms and findings, of which the small myomas make up only a small part of the gynecologic condition as a whole. Ordinarily, the uterus with small myomas should be observed by palpation at six month intervals, as a part of the general follow-up of the patient. On the other hand, some physicians tend to be too conservative in contrast to the rapid surgeon, and may neglect to point out the value and importance of pelvic surgery in the individual case. The ultraconservative may cause as much harm as the "knife-happy" surgeon.

Hormone therapy for myomas has been suggested by a few enthusiasts. All agree that estrogen should be avoided, as this hormone causes the myomas to grow further. Because Lipschutz found that progesterone protected against, or caused regression of, the muscle tumors produced by estrogens in the esophagus and gastro-intestinal tract of the guinea pig, a few have reported that progesterone caused regression of myomas in women. This is improbable.

Androgens have been used to reduce the size of myomas to make surgery easier, to reduce blood loss from meno-metrorrhagia, to allow anemia to be relieved, and for temporizing when patients are poor operative risks (Haskins). Undoubtedly reduction in size and amount of bleeding follows the direct neutralization of estrogens and the depression of the pituitary and ovary. But a sufficient amount of androgen, as testosterone propionate, twenty-five or fifty milligrams two or three times weekly, or methyl testosterone ten to thirty milligrams daily, to produce these beneficial changes, will cause degrees of virilism, with growth of hair on the face, increased acne, some deepening of the voice, and enlargement of the clitoris. These changes are undesirable, and not all will regress after cessation of the treatment. In an occasional case, especially when the patient is a poor operative risk, this treatment may be used to temporize until the menopause occurs.

Myomectomy, whether single or more often multiple, is advisable when possible, certainly in younger women, particularly those who desire children, with conservation of a reasonably normal uterus. Myomectomy is always indicated when operation must be performed during pregnancy. Operations during pregnancy are performed when the tumor is discovered to be of quite some size, particularly filling the true pelvis, or when it extends to one side in the pelvis, of eight to ten centimeters in diameter, and when associated with pelvic pain. If there is no bleeding, and no apparent threatened abortion, the operation often can be performed without causing miscarriage, even though rather extensive dissection of the uterus may be necessary. If there is any threat of abortion before the operation, as indicated by cramping, pain, or scant bleeding, then any operative procedure often will be followed by loss of the pregnancy.

The treatment of myomas of the uterus by hysterectomy has certain rather definite guide posts. *Menometrorrhagia* of sufficient degree to cause secondary anemia is one indication for hysterectomy, although at times unusually profuse and distressing menstrual flow may occur without causing obvious anemia. Evidently in such cases the woman's bone marrow is able to reproduce the blood at a remarkably rapid rate. More often, there are varying degrees of anemia, because each month her bone marrow cannot produce quite enough blood to catch up with the loss from the month before. Not always does marked blood loss, associated with small myomas, necessitate hysterectomy, because curettage of the uterus alone, or followed by thyroid extract therapy when indicated, the reduction of weight in the obese, the treatment of asthenia in the malnourished, and an aid to the relief of nervous tension by means of phenobarbital or the tranquillizing drugs, may be followed by normal menstruation. On the other hand, if in spite of these conservative measures, the menorrhagia continues and is a source of fatigue, exhaustion and concern to the patient, hysterectomy is indicated.

Secondly, if there is *pain* in the pelvis, intermenstrually or with menstruation, of incapacitating degree or to an extent to interfere with normal actions and relations of this patient, and if the pain can reasonably and carefully be associated directly with the enlarged uterus, then hysterectomy is indicated. If the pain is relieved by mild sedation, or reassurance of the absence of malignancy or serious disease, or if other reasons are found for the pain, naturally hysterectomy is not indicated. Careful consideration of the pelvic pain, usually by more than one interview and examination, may allow one reasonably accurately to determine the results to be obtained from hysterectomy.

The third reason for hysterectomy includes the growth and *size* of the uterus. It is the general opinion that if a uterus is the size of a three month's pregnancy or larger, due to myomas, that hysterectomy is justifiable. There are exceptions. Some patients cannot accept a major operation, or the loss of the uterus, and are better observed, even though the tumor is of an undesirable size. As a rule, the patient will accept this indication and will be pleased to be rid of the mass.

Also associated with this point of the size of the tumor, is the rate of growth. If the rate of growth is quite rapid, then hysterectomy is indicated, because one must realize the possibility of sarcomatous change in a myoma. While this change is relatively rare, it is not to be discounted. The removal of a uterus after the menopause, when myomas are first discovered, usually is not indicated, unless the uterus is quite large, unless there are some symptoms of discomfort or there has been some postmenopausal bleeding. If there is any reason to believe the tumor mass has been enlarging, as suggested in increasing pelvic symptoms, then hysterectomy should be performed. Sometimes one may choose to observe the mass over a month or two, or several months, to determine that there is being some progression in size. While one tends to observe, in some instances the careful history may mitigate against delay.

While the profession as a whole, and the gynecologists in particular, deplore the surgical operation that may be avoided, on the other hand, it is so important not to overlook malignancy in the pelvis, and not to avoid pelvic surgery when great relief may be obtained.

ADENOMYOSIS OF THE UTERUS

Adenomyosis is the growth of the basalis of the endometrium into the myometrium, consisting of the endometrial glands and surrounding stroma, and accompanied by a peculiar proliferation of fibrous and muscle tissue, which has no pattern with relation to the normal myometrium. Adenomyosis was known first as adenomyoma, being described by Rokitansky in 1860. From 1890 to 1905, von Recklinghausen was particularly interested in the adenomyoma and believed that the glands found in the wall of the uterus represented remnants of wolffian duct tissue, and that these glands were not connected with the endometrium. At that time, Cullen in this country wrote several papers, showing that adenomyoma was directly connected with the endometrium itself, being a down-growth of the basalis into the myometrium. Cullen reported some cases with very marked adenomyosis, which had extended entirely through the wall of the uterus into the cul-de-sac and into the rectum. Evidently he believed that all the nodules of endometriosis in the cul-de-sac and wall of the rectum were related to direct invasion from the endometrial cavity, so that these nodules were called adenomyoma of the rectovaginal septum and adenomyoma of the sigmoid. It was not until 1921 that Sampson began to clarify the present concepts of external endometriosis.

Today we would use the term adenomyoma for a reasonably encapsulated isolated rounded nodule within the myometrium, composed of adenomyosis with endometrial glands, stroma and surrounding new formation of connective tissue and some muscle tissue. Ordinarily speaking this has no connection with myoma of the uterus, although in exceedingly rare instances one may find a few endometrial glands within a myoma, and one would think that such glands had grown into the myoma by direct extension. The more usual finding is a diffiuse growth of endometrium into the uterine wall, which may extend completely around the endometrial cavity, or may extend more into the anterior or posterior wall. This adenomyosis is often more marked in the anterior wall.

The term internal endometriosis has been used to mean adenomyosis or the growth of endometrium in the uterine wall. While this term is correct, it does connote that there is a connection between internal and external endometriosis, which, if true, is very difficult to understand. The cause of internal endometriosis is not clear; it may be related to congenital displacement of endometrial glands, or their growth from embryonic remnants in the myometrium, or from hormone stimulation. The latter seems somewhat more likely, but there are probably other unknown factors.

Adenomyosis is found more often in women in the late thirties and in the forties. In all uteri removed for pathological reasons, fifteen to twenty per cent have adenomyosis (Dockerty). This makes a very respectable percentage of cases with this disease, indicating its importance, but it is not nearly as frequent as myomas of the uterus, which probably are found in more than fifty per cent of hysterectomy specimens. The disease is rarely found before the age of thirty years, evidently a considerable time being required for its development. After the menopause, and after estrogens have regressed, the atrophy of the uterus includes atrophy of the adenomyosis, so that it becomes entirely asymptomatic. However, it could be stimulated and returned to its premenopausal condition by sufficient or excess estrogenic therapy.

The pathology of adenomyosis is largely encompassed by the definition of the disease. The basalis of the endometrium, which is the origin of the later differentiating and functioning superficial epithelium, does not respond to progesterone, but it is stimulated greatly by estrogen. For some unknown reason, the basalis turns and invades the myometrium, including the glands and their surrounding stroma. These invade in a very circuitous manner, apparently being pressed from one direction to another by the blood vessels and muscle bundles, so that they wind back and forth. Only occasionally do they extend to the serosa of the uterus, where they may possibly perforate and show implants of the typical purple granular character on the surface of the uterus.

As the glands and stroma grow, there is produced a fibrous tissue reaction, which surrounds these islands in an irregular manner. Apparently within this connective tissue there may appear some new muscle cells. The invasion of the glands and their surrounding stroma may extend diffusely around the uterine cavity, causing a globular enlargement of the uterus of one and one-half, two or three times normal size. Or the endometrium may extend more into the anterior wall or the posterior wall, causing an asymmetrical enlargement, and this particularly seems true of the anterior wall.

The glands in the adenomyosis are of the basalis type, containing a lining epithelium of non-secretory, tall, bluish epithelial cells. These glands are similar to the basalis in another respect, in that only a small percentage of cases show any secretory changes when there is a late interval or premenstrual endometrium. In only occasional instances does one see the basal globules, or saw-tooth glands, that may occur with premenstrual endometrium. But there are two reasons for this: the glands and stroma of adenomyosis arise from the basalis and do not react to progesterone, and secondly, an analysis of cases with adenomyosis shows an increased percentage with endometrial hyperplasia or anovulatory endometrium with no evidence of progestational effects. This suggests that ovulation and corpus luteum formation occur less frequently in these cases. This was reported by one of our third year students, Spatt in 1946. He analyzed fifty-two cases with adenomyosis of the uterus and found endometrial hyperplasia or anovulatory interval non-secretory endometrium in thirty-one. The date of the last menstrual period, before hysterectomy, indicated that twelve cases with non-secretory endometrium should have shown definite secretory endometerium. In only eight cases (fifteen per cent) was a secretory endometrium present. On the other hand, it is well known that during pregnancy, when tremendous amounts of progesterone are present, the stroma in areas of adenomyosis always forms a decidual appearance and the glands are lined by rather low cuboidal epithelium, being exhausted of their glycogen. So, these areas are not completely insensitive to progestational effects, but they are relatively so in relation to the normal cyclic effects in the non-pregnant state.

Adenocarcinoma must develop occasionally in adenomyosis, as it may in the endometrium, and sarcoma of the endometrial stroma must develop in the stroma surrounding the adenomyosis. However, these two forms of malignancy occur rarely with adenomyosis, or they are not recognized. One may interpret malignancy in the wall as extension from a primary growth in the endometrial lining. That stromatosis (endolymphatic stromal myosis) may develop from adenomyosis, or represent a variant of adenomyosis, in either the benign or rarely malignant state, is possible, but it has strangely different characteristics.

The *symptoms* of the patient with adenomyosis include dysmenorrhea and menorrhagia. The dysmenorrhea is thought related to bleeding in the areas of adenomyosis, which is trapped and cannot be extruded into the endometrial cavity and be passed out of the uterus. This may be an explanation, but it is somewhat difficult to understand, because of all cases with adenomyosis that one may inspect grossly or microscopically, most often no blood whatever is seen in these endometrial areas. In others, rarely does blood distend the cavities, as one might expect, if the pressure of the bleeding were the cause of the pain. It is true that in some instances accumulations of blood and minute hemorrhagic cysts do form in the wall of the uterus. It is also peculiar that anovulation and endometrial hyperplasia are so frequently found with adenomyosis, though by no means uniformly so, and that these conditions are not associated with dysmenorrhea.

The other fairly characteristic symptom is menorrhagia, profuse and prolonged, but regular menstruation. Actually, there may be metrorrhagia present, though this is less characteristic. One would think metrorrhagia would occur more often due to the increased incidence of anovulatory endometrium and endometrial hyperplasia. The cause of the menorrhagia may be related to the disruption of the normal musculature of the uterus, perhaps interfering with normal contractility of the myometrium and the contractibility of the blood vessels supplying the endometrium. This is conjecture.

Any other symptoms associated with adenomyosis are related to the weight and enlargement of the uterus, which may add to its displacement, retroversion, and first or second degree descensus of the uterus. These include bearing-down pressure discomfort, dyspareunia, and even sterility.

The diagnosis of adenomyosis is never an accurate one, but is one of suspicion. The finding of an enlarged symmetrical uterus, or one with slightly increased bulge in the anterior wall, associated with dysmenorrhea and menorrhagia, always suggests the possibility of adenomyosis, but there may well be an intramural myoma, or a submucous myoma, or simply some diffuse enlargement of the uterus without any other lesion. Since the adenomyosis is often associated with other lesions in the pelvis, including myomas and adnexal diseases, the separate diagnosis of adenomyosis may be over-shadowed by the combination of complaints and findings in the pelvis of the individual patient.

It has been shown that the hysterogram, obtained by injecting a water-soluble radio-opaque medium into the uterine cavity may demonstrate small sinus tracts extending into the myometrium in about fifteen per cent of patients with adenomyosis. This is diagnostic, but not of too much practical importance.

There is no specific *treatment* for adenomyosis of the uterus except hysterectomy. Obviously, since this condition is essentially a benign one, though malignancy may possibly occur on rare occasion, if the diagnosis is entertained, if the symptoms of pain and bleeding are not too severe and incapacitating, and if they may be aided by mild sedation, analgesics, curettage, or small doses of testosterone in occasional instances, perhaps the patient can tide along for a period of years, or even until her menopause, without the necessity of hysterectomy. When the symptoms are quite marked, do not respond to conservative therapy, and interfere with the normal pursuits of life, laparotomy is indicated. In an occasional case, one may find the anterior wall, or perhaps the posterior wall, peculiarly and particularly enlarged from the thickening of adenomyosis. This area may be excised by an eliptical incision, extending down to the endometrium, and the wall may be closed in layers with catgut sutures. One may possibly excise all of the involved area. More often the involvement is so diffuse, though perhaps of less degree in other areas of the uterine wall, that the local excision is not a satisfactory solution. After such an excision, this uterus might possibly be of use for a subsequent pregnancy. More often the only cure is hysterectomy, which is largely understood by the patient and physician before the operation is performed. The patient, who has accepted the procedure of a major operation for the purpose of obtaining relief from severe symptoms, as a rule, understands and desires hysterectomy.

SUBINVOLUTION OF THE UTERUS

Subinvolution of the uterus is a diffuse enlargement of the uterus, which has resulted from inability of the organ to regress to its normal size following a pregnancy. Immediately after the delivery of a full term pregnancy, the uterus contracts, forming a large mass, rising to the level of the umbilicus, prominent and firm. A remarkable regression occurs in the next two weeks, in which the reduction in size approaches the normal non-pregnant state. After four to six weeks from delivery, palpation of the uterus gives the impression that it is of essentially normal size, although if one inspected the uterus by opening the abdomen, generally it would prove to be slightly enlarged.

From three to six months after delivery the uterus does revert, under normal circumstances, to an entirely normal size. The marked congestion or great vascularity of the organ and surrounding tissues has disappeared. It is for this reason that elective surgery in the pelvis is delayed for three months, and preferably six months after delivery. This extra-ordinary reduction in size of the uterus does not progress to a normal degree in a small percentage of women, perhaps ten or twenty or thirty per cent. The reason for the inability of the uterus to shrink to normal size is unknown. Various obstetrical delays and complications may have some association, but these are not clearly demarcated.

Retroversion of the uterus, which may form as soon as the uterus has reduced enough to fall back into the hollow of the sacrum may be a factor in subinvolution, because the torsion of the blood vessels, and the position of the uterus may allow continued congestion, or dilation of the veins of the uterus, so that there is some obstruction to the circulation.

The pathology of subinvolution of the uterus is not too clear, but special stains (Masson's trichome stain and others) indicate increased amounts of elastic tissue. Particularly this elastic tissue remains about the blood vessels. Ordinarily, following delivery, the extremely large amount of elastic tissue formed during normal pregnancy essentially completely disappears.

In the first few months after delivery, varying degrees of subinvolution may regress further, both spontaneously and by means of treatment, but after a few months the majority will make no further improvement by any means.

More often there are no *symptoms* from subinvolution of the uterus, and frequently the palpation of the uterus of parous women shows varying degrees of enlargement, of one and one-half times normal size, or two or three times normal size. Sometimes this enlargement, found on a single examination, is related to "pelvic congestion," of whatever origin that may be, or to engorgement related to the menstrual cycle, especially immediately before menstruation. Therefore, it is so necessary to examine a patient on more than one occasion, to determine the permanency of any enlargement. In some patients, however, the enlargement and heaviness of the uterus tends to carry the uterus into retroversion, and to produce descensus of first or second degree. Often there are associated degrees of cervicitis, cystocele, rectocele, and relaxed vaginal outlet. With combinations of these findings there may or may not be symptoms. The symptoms include bearing-down, pressure discomfort, heaviness in the pelvis, dyspareunia, discharge and abnormal bleeding. Abnormal and irregular bleeding rather frequently may be associated with subinvolution of the uterus, although by no means do all cases have any symptoms whatever.

The *diagnosis* of subinvolution of the uterus is made by the finding of an enlarged uterus, definitely and continuously enlarged on repeated pelvic examinations at different times of the cycle, and by the fact that the patient has had one or several children, with perhaps the appearance of symptoms following the delivery of the children. Often there is retroversion of the uterus due to enlargement and congestion, associated with weakness of the supporting ligaments. The occurrence of subinvolution is somewhat vague, and the incidence varies from one observer to another. The symptoms may be difficult to evaluate. The differentiation from myoma of the uterus, whether intramural or submucous, from adenomyosis with diffuse enlargement of the uterus, and from fibrosis, may be difficult or impossible to determine. The impression is a clinical one, which one well knows may be in error.

The *treatment* of subinvolution of the uterus is in two parts, the early and the late treatment. Soon after delivery, in the first few weeks, if the uterus seems quite enlarged, particularly six weeks from the time of delivery when it should have returned to normal size, if it is in proper position, then ergotrate, methergine, or other uterine muscle oxytoxics, should be given for three or four days, to be repeated if necessary in two to four weeks. This treatment may be followed by remarkable improvement in some cases. Particular indications for such treatment include pelvic discomfort, pelvic pressure, a sense of heaviness and dropping, and perhaps some slight irregular bleeding. If there is irregular bleeding the presence of retained placenta is always to be suspected. If improvement does not follow the ergot drugs, curettage may be performed. In fact, curettage may be followed by considerable reduction in the size of the uterus, particularly when performed in the first few months following a pregnancy.

At six weeks from delivery, if the uterus is found retroverted and definitely enlarged, then one should attempt correction. The patient is urged to use the knee-chest position once or twice daily for five or ten minutes, and if the uterus can be raised into normal position a Smith or Hodge pessary is inserted. She is requested to wear the pessary if not uncomfortable, and usually to continue the knee-chest position once daily. The pessary is removed, cleaned, and re-inserted at six week intervals. This may be followed by marked reduction in size. Perhaps this results from the relief of congestion and not the absorption of elastic tissue of subinvolution. Later the pessary is removed, the uterus allowed to fall into the retroverted position, if it must, and no further treatment is necessary unless there are recurrent symptoms.

In the patient with chronic subinvolution of the uterus, most often no treatment is indicated. The routine examination of a large number of parous women shows varying degrees of enlargement of the uterus following delivery of one or several children. Only when there are positive symptoms, which are usually associated with various other pathological findings in the pelvis, would one consider any surgical approach. Ergotrate, curettage, and pessary, are of little value in the treatment of chronic subinvolution. Hysterectomy is indicated only when there are positive and serious symptoms, associated with definite enlargement of the uterus. If the symptom consists primarily of irregular bleeding, as a rule, curettage should be performed; it is remarkable how many patients have improvement of the bleeding with this simple procedure, to say nothing of the important point of investigation for malignancy. If there are related findings of retrodisplacement, descensus, cervicitis, cystocele, rectocele and relaxed vaginal outlet, then there is a "combined syndrome" of multiple diseases and abnormalities, and when associated with definite and distressing symptoms, an indication is present for one of the most popularly performed surgical operations, vaginal hysterectomy and cystocele and rectocele repair.

FIBROSIS OF THE UTERUS

Fibrosis of the uterus is an enlargement of the uterus produced by an increased amount of connective tissue, placed diffusely throughout the wall of the uterus. The cause of this condition is unknown, and its differentiation is difficult. It is impossible to differentiate from subinvolution of the uterus, unless special stains (as Masson's trichrome stain) may be made of microscopic sections of the uterine wall. Many pathologists and gynecologists may discount the importance and frequency of fibrosis of the uterus, and feel that it is of no real clinical importance, and that the variations in size of the uterus with fibrosis, or subinvolution, are within normal limits, and are to be disregarded as of any important clinical significance.

On the other hand, many believe that fibrosis of the uterus is an entity, though not well understood. It occurs more in the latter part of the child-bearing period, that is from thirty-five to fifty years of age, and is reduced in size after the menopause. It is not particularly frequent, at least to be of real clinical importance alone. The *pathology* of fibrosis of the uterus, as stated above, reveals a diffuse enlargement of the uterine wall, due to an increase in connective tissue. Special stains show this is not due to an increase in elastic tissue, but of the non-elastic fibers.

The *symptoms* of fibrosis of the uterus are those of any enlargement of the uterus, which cause it to become heavy, frequently displaced, either into retrodisplacement or as descensus of the uterus. There may be associated menorrhagia or metrorrhagia. The patient may complain of pelvic pain, pressure, bearing-down and fallen sensation. On the other hand, the mere finding of a diffuse enlargement of the uterus is no indication for any surgical procedure, unless there are definite and positive symptoms associated with it.

The *diagnosis* of fibrosis of the uterus is impossible to make, but may be suspected in certain instances. The differentiation from subinvolution is possible only if one is certain the enlargement developed after observed normal involution from pregnancy, or if there is enlargement of the uterus with no previous pregnancy. The differentiation from adenomyosis, or intramural and submucous myoma, may be difficult or impossible to make. As a rule, the symptoms of menorrhagia and dysmenorrhea are not marked with fibrosis of the uterus.

There is no indication for any *treatment* of fibrosis of the uterus unless there are associated severe symptoms. When such symptoms do develop, they may include irregular bleeding, for which curettage would be indicated, which may be followed by improvement and slight decrease in the size of the uterus, though one would doubt a regression if there were true diffuse scarring of the uterine wall. When hysterectomy is necessary, there are usually additional findings, as with subinvolution, namely, retroversion of the uterus, descensus of the uterus, and often cystecele, rectocele and relaxed vaginal outlet. When these findings are present and there are no symptoms, then no surgery is indicated. But if there are definite and positive symptoms of bearing-down pressure pain, dysmenorrhea, menometrorrhagia, dyspareunia, and often stress incontinence and dyschizia, then surgery is indicated, particularly vaginal hysterectomy with cystocele and recotcele repair. In some instances hysterectomy might be necessary without any repair work indicated, and abdominal hysterectomy might be the better approach.

Fibrosis of the uterus is a rather indefinite clinical disease, and such a diagnosis will not be entertained with any great frequency.

PELVIC CONGESTION: THE CONGESTION FIBROSIS SYNDROME

Some fifty years ago pelvic congestion was a term used to explain various and vague pelvic and nervous complaints in women. It was thought to explain dysmenorrhea, metrorrhagia and pelvic pain. Evidently the confusing diagnosis was used for many of the better understood diseases today. Through the years this concept of engorgement of the pelvic blood vessels has been used to explain lesser and vague pelvic complaints, although many have completely discounted this theory. The concept of varicose veins in the pelvis, particularly varicose veins in the broad ligaments, was thought to explain many and various aches and pains in the pelvis, and many dysfunctions. These varicose veins were said to be palpable as a soft, bulging, worm-like mass in the broad ligament areas, palpable by some, but discounted by others. Many operations have been performed to ligate and excise these varicose veins.

In the past few years, the concept of pelvic congestion has been brought to the fore by Howard Taylor, Jr., and he has made a rather good case for it. The thought is that, in many women with marked nervous tension and various anxieties, probably the autonomic nervous system is off balance, causing the pelvic blood vessels to become dilated, with congestion and stasis of blood in the pelvic veins, causing subsequent enlargement of the uterus, with fullness of the ligaments, and even edematous swelling of the ovarian tissue. That such changes may cause pelvic discomfort, pressure, abnormal bleeding, dysmenorrhea, and dyspareunia, has been accepted by some enthusiastically and by others with reluctance, and a part of the profession remains skeptical.

The pathological changes that may develop in this situation are not distinctive. Inspection of the pelvis, at operation, shows enlargement of the pelvic veins in the ovarian pedicle, in the communicating vessels from the ovary to the uterus, and in the uterine veins in the broad ligaments. The uterus shows varying degrees of enlargement, sometimes two or three times normal size, and appears rather soft and slightly bluish (hence the term pelvic congestion). The microscopic studies of the uterus and endometrium show no characteristic findings.

Associated with these symptoms and findings, as a rule, there is general asthenia, loss of weight, and even degrees of malnutrition. Commonly there is general pelvic relaxation, with a first or second degree descensus, often retrodisplacement of the uterus, and frequently relaxed vaginal outlet, with cysto-

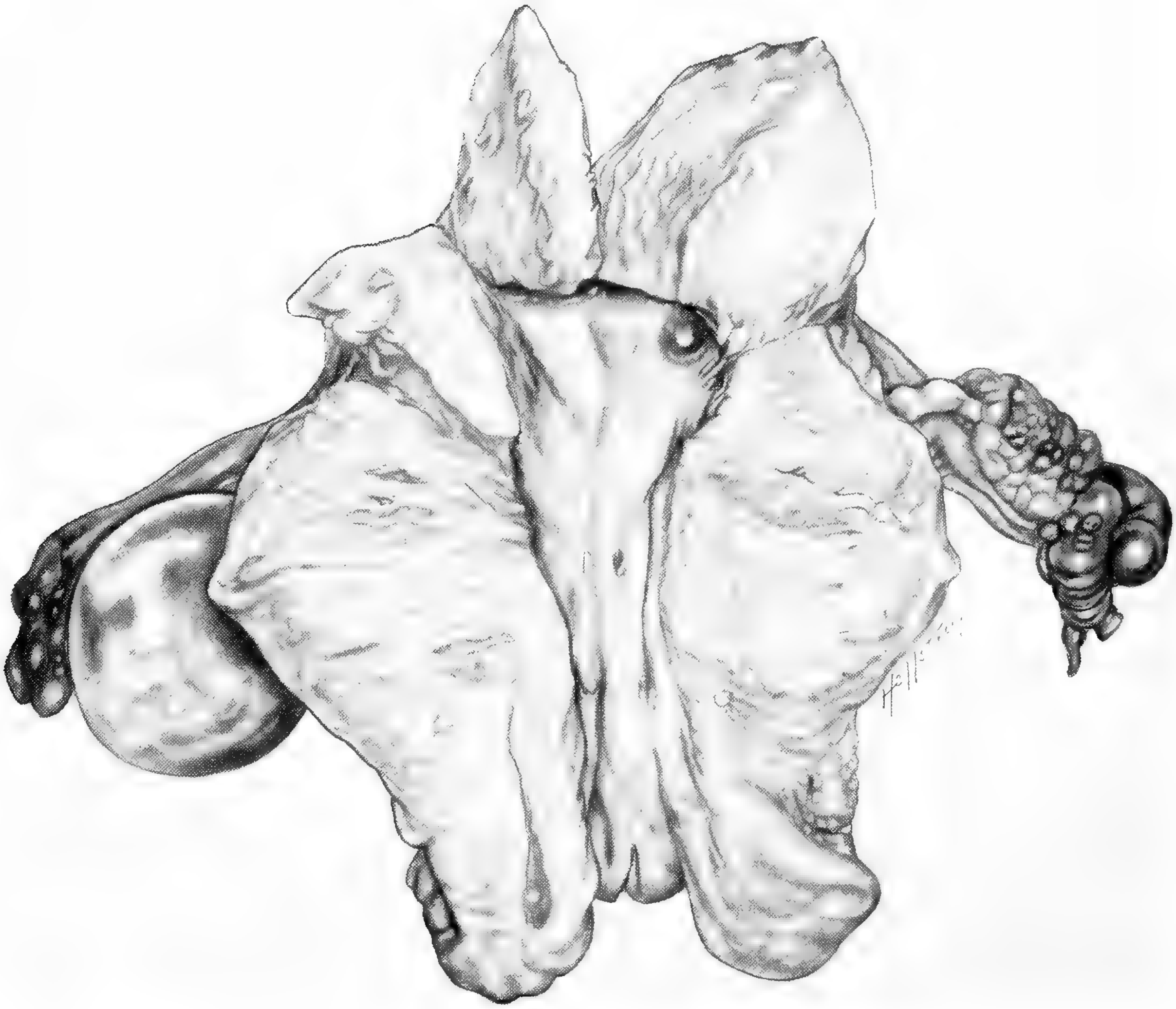

Fig. 149. Hyperplasia of the uterus, with fibrosis and subinvolution, age forty-seven years. Prolonged metrorrhagia, not relieved by curettage on two occasions. Atypical endometrial hyperplasia. Follicular cyst, ovary left, atrophic ovary right.

cele and rectocele. Some have felt that the asthenia and general pelvic relaxation, associated with the functional effects of nervous tension and anxiety, are explanations of the symptoms, and that there is no necessity for coining the term "pelvic congestion", which suggests some separate disease process in the pelvic organs.

The *symptoms* are those of pelvic discomfort, perhaps marked, more often vague and dull, and at times incapacitating. Associated with the functional complaints of dysmenorrhea and abnormal menstruation, commonly the patient complains of exhaustion, backache, headaches, dyspnea, and any of the other functional complaints to which the human race is subject.

The *diagnosis* is largely one of exclusion. First, the numerous complaints are sifted apart, the general examination shows weight loss and loss of muscle tone, and the pelvic examination shows degrees of relaxation, and particularly some enlargement and tenderness of the uterus, with no obvious adnexal pathology. Some observers may note a fullness in the broad ligaments. The size of the uterus tends to vary considerably. Particularly before menstruation the uterus may seem unusually enlarged, and it may seem unusually large at repeated examinations in the menstrual cycle. On later occasions, the uterus may become permanently enlarged to some degree by fibrosis, due to chronic congestion, which gives the name "congestion fibrosis syndrome."

The *treatment* primarily is one of treating the nervous tension and anxieties. The most important approach is by a sympathetic and understanding attitude, by repeated interviews in which the patient is allowed to discuss her problems, followed by advice as to hygiene, physical exercise, and diversified activities and interests in life. Mild sedation, as with phenobarbital, grains one-fourth three times daily (if there is no tendency to depression), or the various tranquillizers, may be helpful during periods of observation. Reassurance as to the pelvic findings, curettage for abnormal bleeding, and the use of pessaries for descensus and retroversion may add to the general comfort and well-being.

In certain instances the degree of descensus and general pelvic relaxation, and the associated menorrhagia, dysmenorrhea, dyspareunia, and even the fear of pregnancy in later life, are of sufficient importance that hysterectomy and proper reconstructive surgery of the pelvic floor are indicated. However, the functional background must be carefully considered by the physician and the patient, who must understand the interrelated causes of the pelvic complaints. With proper choice of cases and under the correct circumstances, pelvic surgery and understanding by the patient may give a gradual and excellent improvement. Cases of this type require extra effort on the part of the physician and understanding by the patient.

SARCOMA OF THE UTERUS

Sarcoma of the uterus occurs in three forms, as a malignant change in the smooth muscle cells or the connective tissue cells of the myometrium, in the cells in myomas of the uterus, or in the stromal cells of the endometrium. A fourth type of sarcoma is the mixed mesodermal tumor, which will be considered under a separate heading. Sarcoma of the uterus occurs mainly after the age of thirty-five years, most commonly between forty and fifty years and definitely may occur as a postmenopausal disease.

Sarcoma of the uterine wall is classified as *primary* and *secondary*. The primary tumor arises in the myometrium, apparently directly from the muscle cells. As to whether the malignancy can arise from the mature muscle cells or from some immature embryonic cells that may persist is conjectural. There remains a possibility that the growth arises from the connective tissue of the uterine wall, but histologic study over many years seems to indicate that the normal muscle cells melt directly into the malignant cells. Since the muscle cells, and connective tissue, and the blood vessels are mesodermal in origin, perhaps all may contribute to the origin of sarcoma of the uterus. Approximately one-third of cases of sarcoma of the uterus are said to be of the primary type.

Secondary sarcoma of the uterus indicates a sarcomatous change in a preexisting myoma, and the majority of sarcomas of the uterus arise in myomas. It has been considered that one in two hundred cases with myomas of the uterus will develop sarcomatous change, but from our material, it appears that about one in one hundred excised uteri (some without myomas) will show sarcomatous change. In both the primary and the

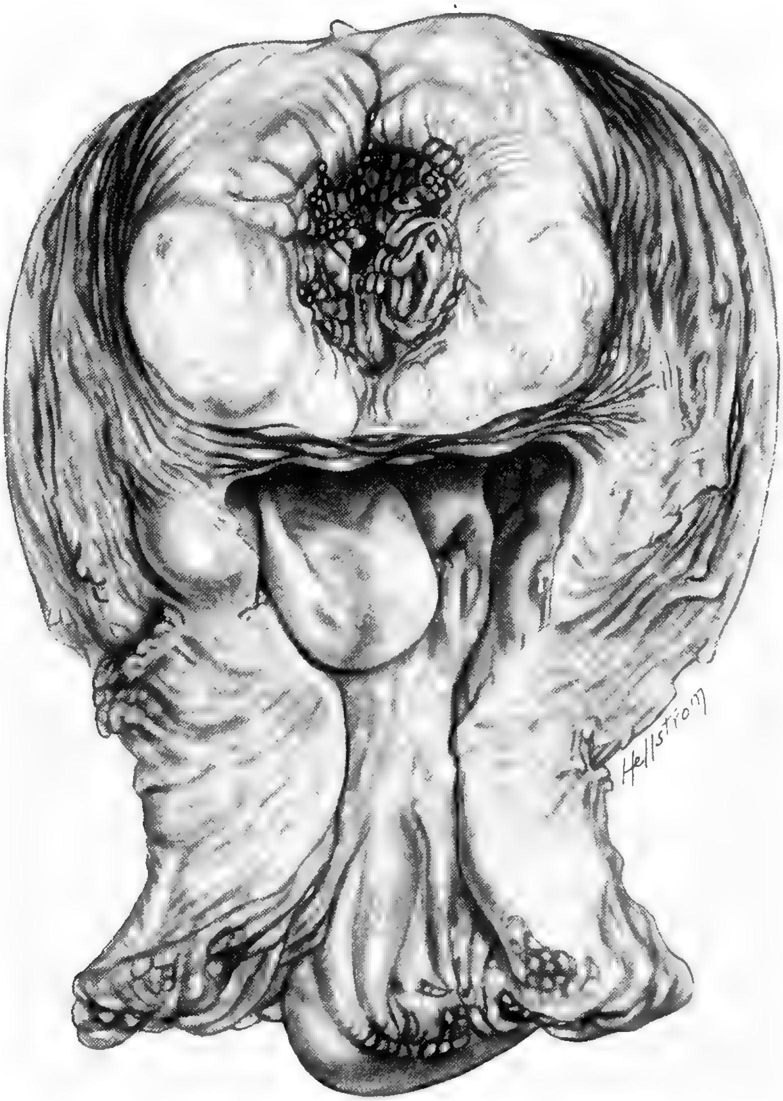

Fig. 150. Sarcoma in myoma. Incidental finding and appears as reddish necrotic area. Also present are other small intramural and submucous myomas. The latter appears unusually flattened.

secondary type the sarcoma cells more frequently seem to arise from the muscle cells themselves, and form the spindle-cell type of sarcoma. Sometimes the elongated cells are very small and tightly packed together, but in other instances they are quite enlarged with particularly large nuclei. The nuclei in both instances stain prominently and mitoses are frequent. It has been pointed out (Novak) that the number of mitoses are directly related to the degree of malignancy, but there is some doubt in this as a conclusion. The mitoses may be normal-appearing mitoses, with well formed spindles, indicating quite rapid growth, but there are always numbers of abnormal mitoses, in some areas being quite prominent, forming giant nuclei and irregular masses of chromatin which divide in an asymmetrical manner. Another microscopic form is the round cell sarcoma, in which the nuclei are closely packed together, and the cytoplasm sur-

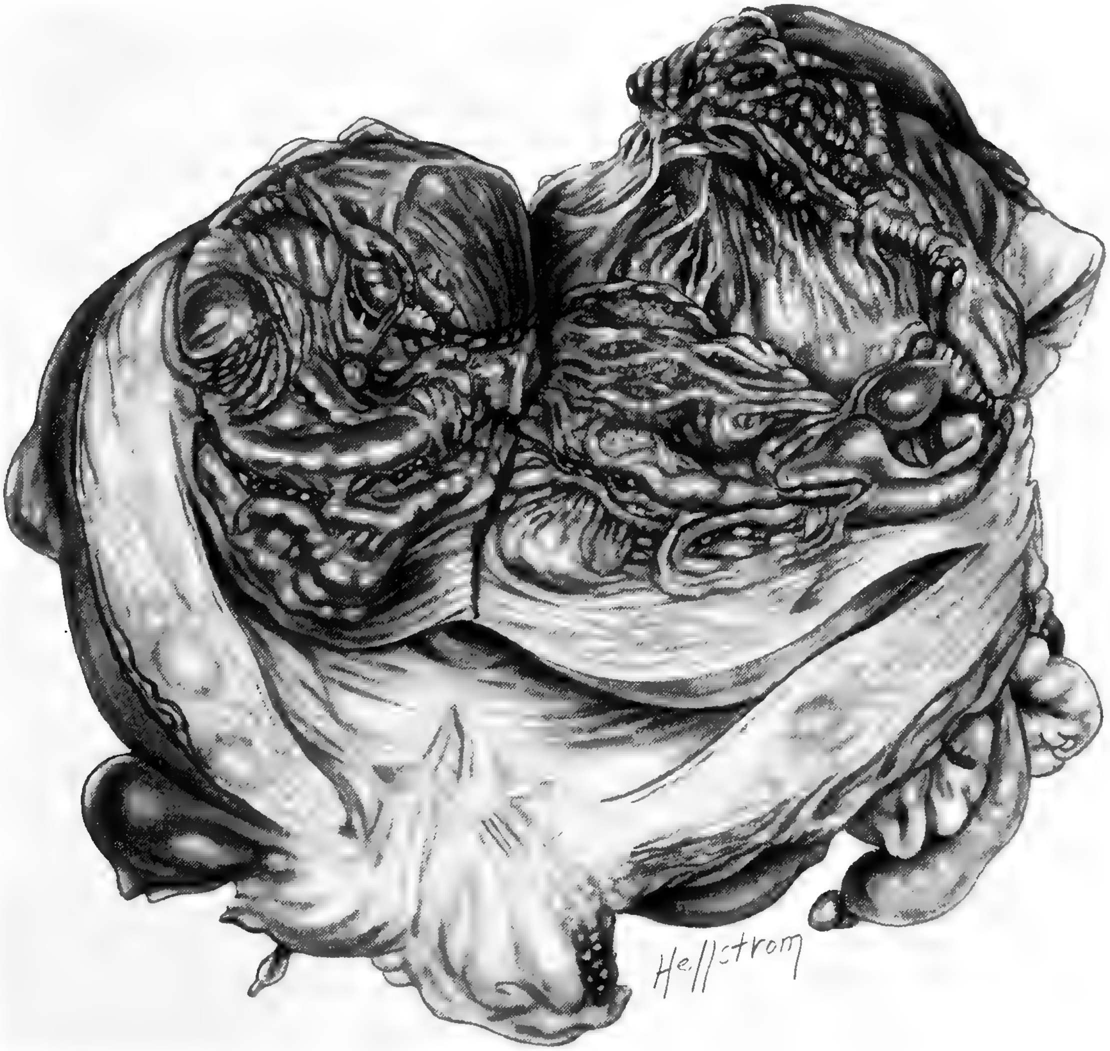

Fig. 151. Sarcoma in myoma, meaty red, sometimes pink or yellow in color, with degrees of necrosis. In this case, the adnexae also were removed. Patient died two years later with pulmonary metastases, apparently arising from this tumor.

rounding the nucleus is scant. Sometimes this appearance is presented by a transection of the elongated spindle cells. Another form is the giant cell type of sarcoma with extremely enlarged nuclei. Some scattered giant cells are presented in most of the more malignant spindle cell types. Other types have been described from the microscopic appearance, but they are infrequent.

A finding known as the cellular myoma may be confused with sarcoma in a myoma. In this instance, the cells are quite closely packed together, have very small portions of cytoplasm, and often give the impression of a round cell sarcoma; there may be scattered mitoses through this cellular change. And yet this is a benign tumor, though apparently more rapidly growing than the ordinary myoma. As to whether this may represent a pre-malignant form must remain conjectural, but once this tumor is removed, it does not recur.

There are evident differences in various sarcomas of the uterus. Some of the well-formed ones are extremely malignant and fatal in a high percentage of cases. On the other hand, a somewhat larger number of cases have a better prognosis. They are diagnosed as sarcomatous changes in myomas, with definite microscopic changes of malignancy, with marked increases in mitoses and some irregularity of the cells. But these changes, when discovered unsuspectedly in the depth of the myoma, rarely are followed by a recurrence or a fatal result after hysterectomy. The gross appearance of the myoma in these instances as a rule is not unusual, and no clinical suggestion of malignancy is present. On the other hand, those sarcomas which show an obvious gross change in the uterus, which have an appearance of raw meat, with a yellowish mushy appearance and marked necrosis, with a history of rapid enlargement of the uterus,

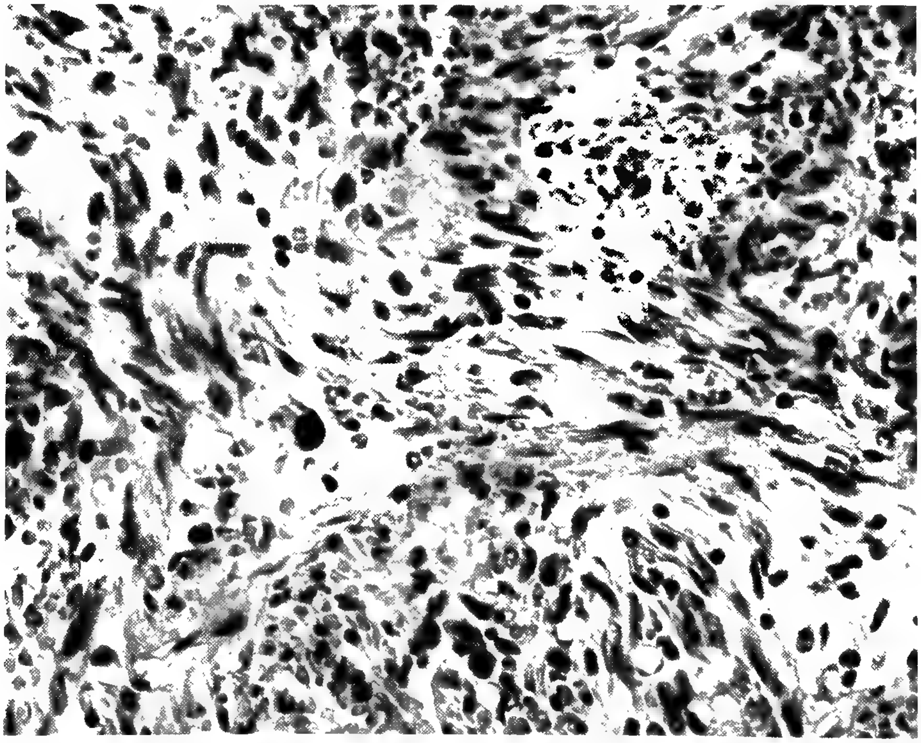

Fig. 152. Sarcoma of the uterus. This remarkable disorganized appearance of the muscle and connective tissue cells of this malignant tumor, arising in a myoma, shows great variation in size and shape of the nuclei, the presence of giant nuclei, and markedly irregular and prominent mitoses.

and often with some irregular or postmenopausal bleeding, have an extremely serious portent. The disease is more serious when occurring after the menopause. The short history over a few months, the increasing pelvic pain, bleeding and the appearance of an obvious distending tumor means an almost invariably fatal outcome, regardless of a wide hysterectomy and bilateral salpingo-oophorectomy. The addition of deep x-ray therapy apparently is of little value. The tumor extends through the pelvis and metastases occur to the liver, lungs, mediastinal nodes, neck and elsewhere. The course of this disease in these latter cases is rather rapid over a few months.

The more frequent incidentally found and less anaplastic sarcomatous change in a myoma has an excellent outlook for cure, when hysterectomy is performed without suspicion of malignancy. But when there is the clinical picture of sarcoma of the uterus with obvious recent gross changes, and with microscopic findings of marked necrosis and extreme irregularity of cells, then the degree of malignancy is much higher, and fatal results will approach one-hundred per cent.

The *symptoms* of sarcoma of the uterus are not distinctive. When this malignant form occurs before the menopause, in a majority of cases the patient had a hysterectomy performed for myomas of the uterus. That the tumors were enlarging progressively may not have suggested malignancy. Irregular bleeding from associated myomas is expected. Unusually rapid growth might cause some suspicion of sarcoma. But when the sarcoma develops after the menopause the distinctive symptoms are more obvious. The presence of abdominal pain, the enlarging tumor, and possibly bleeding, cause a strong suspicion of sarcoma, whether of the primary or secondary type. The preoperative *diagnosis* is related to the rapidity of growth, particularly when occurring after the menopause.

The *treatment* of sarcoma of the uterus is total hysterectomy and bilateral salpingo-oophorectomy. For those tumors incidentally found in myomas, when the ovaries have not been removed, then a second operation is not indicated, since most of the incidental sarcomas will be cured by total hysterectomy alone. For those with a preoperative diagnosis of sarcoma, a particularly wide and inclusive operation should be performed. One would even consider the Wertheim operation with pelvic node dissection, if the patient were a good risk for such an extensive procedure. The rapid recurrence of sarcoma of the uterus in the cases with more malignant tumors is a distressing characteristic of the disease. Its shrinkage by deep x-ray therapy gives some temporary relief,

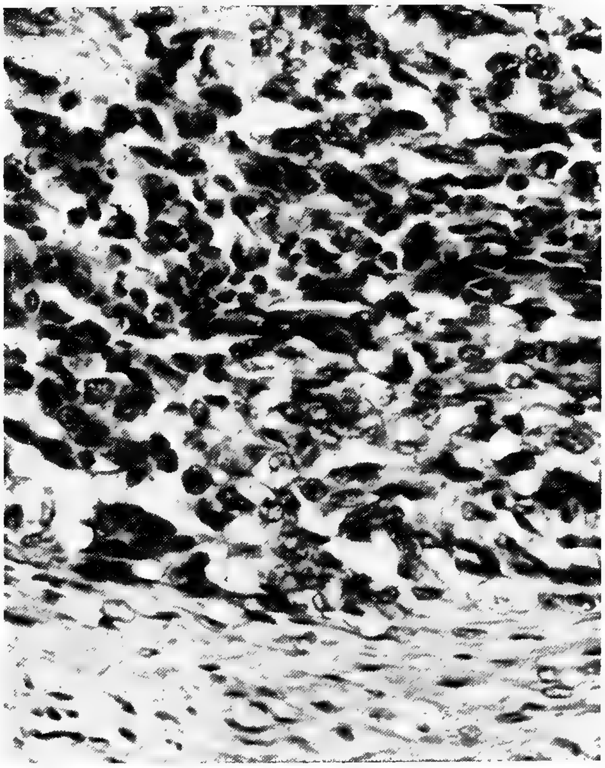

Fig. 153. Sarcoma in a myoma. This malignant change in the myoma shows marked enlargement of the nuclei, many of which are elongated, of bizarre shape, with large masses of chromatin representing the nuclei. There are many abnormal mitoses present, the normal myometrium being pressed into and invaded, as seen at the inferior portion of the photograph.

but generally there is local recurrence and outbreak of metastases in other areas which cause death.

Sarcoma of the endometrium is a rare disease, less frequent than sarcoma of the myometrium, and occurs in middle life. Tumor masses, of polypoid form develop inside the uterine cavity, produce abnormal bleeding and are composed of closely packed cells with deeply stained nuclei and scant cytoplasm, with numerous mitoses, both of the normal and abnormal variety. The tumor may present at the cervical os as a polypoid mass. This tumor invades the uterine wall and metastasizes rather rapidly. The treatment is total hysterectomy and bilateral salpingo-oophorectomy. Recurrence may appear in the pelvis after a short period of time. Results of prompt and wide surgery are encouraging in a smaller percentage of cases. Irradiation therapy is used, but ordinarily is of little curative value.

MIXED MESODERMAL TUMORS OF THE UTERUS

Mixed mesodermal tumors of the uterus include a variety of teratomatous tumors, apparently arising in the endometrium, but sometimes in the wall of the uterus. They appear mainly as a sarcoma of the round cell or spindle cell type, and contain various glands apparently arising from the endometrium, some appearing malignant. They also contain striated muscle cells, many of which appear malignant, with irregular, hyperchromatic nuclei. In addition to smooth muscle, connective tissue, striated muscle, and the glandular elements, often areas of cartilage are found. While this tumor, as a rule, appears in the thirties, forties and after the menopause, it has a prototype that occurs in the very young infant and the young girl, the *sarcoma botyroides.* In the adult, the disease is rather uncommon, but in the child, it is an extreme rarity.

The *pathology* of this type of tumor is variable. In fact, there are several types of tumors that probably fit under this classification. These include the carcinosarcomas, "the collision tumor," and the "composition tumor" of Meyer. A review of cases previously diagnosed sarcoma of the endometrium and sarcoma of the wall of the uterus has shown that many contain striated muscle and glandular elements, and that they belong with the mixed mesodermal group. This group of tumors is highly malignant, extends out into the broad ligaments early, metastasizes to the liver, lungs, cervical nodes, and elsewhere, and has a low rate of cure. The *sarcoma botryoides,* occurring in the very young child, forms grape-like masses, arising in the uterus and cervix, and extending onto the vaginal wall. The polyps are pinkish, edematous, and grossly do not appear malignant. Microscopic sections show a rather loose stroma, the cells of which may show much irregularity of the nuclei, with hyperchromatism, some giant nuclei,

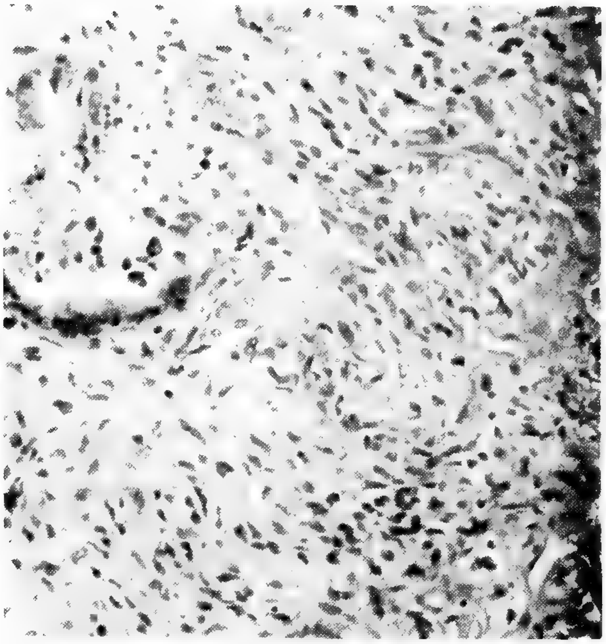
Fig. 154. Mixed mesodermal tumor of the uterus. Irregular connective tissue and muscle cells, with abnormal pyknotic and giant nuclei, have interspersed striated muscle cells and imperfect glands.

and abnormal mitoses. Within the polypoid structures there may be some glandular forms. A careful examination may show striped muscle cells and areas of cartilage.

The *symptoms* of the mixed mesodermal tumors include, as with other malignant tumors of the uterus, vaginal bleeding of irregular character, and pelvic pain when the tumor has become large enough to press against adjoining organs or cause uterine cramping. Examination shows an enlargement of the uterus of varying degree, and often in the adult there is a dilatation of the cervix with the presentation of a tumor mass in the cervical os, or that may be felt high in the cervical canal. In the infant, the symptoms begin with scant bleeding, pelvic pain and weight loss. Examination shows a pelvic mass, and pinkish polyps are found growing from the cervix and upper vagina. This latter tumor may grow rapidly, distend the vagina, and extend widely to the sides of the uterus into the parametrium.

The *treatment* of the mixed mesodermal tumors is surgical, which means abdominal total hysterectomy and bilateral salpingo-oophorectomy. The more wide the dissection the better. The Wertheim excision with removal of pelvic lymph nodes is advisable, as with other malignancies in the pelvis. Preoperative radium has been used, placing radium in the canal and against the cervix, attempting to increase the cure rate, but the cure rate is small, regardless of any treatment. In the infant the recognized treatment is operation, removing the pelvic organs as widely as possible, but in the reported cases most of the results have been fatal, regardless of the treatment. These tumors, in general, are not radio-sensitive, although irradiation therapy is used in desperation.

The mixed mesodermal tumor in the adult probably is not as infrequent as previously thought, because some of the labeled sarcomas of the endometrium and the primary myometrial tumors are of this type.

STROMAL MYOSIS

Stromal myosis is an intriguing disease of the uterus, which has been described under numerous names, since it was first described by Doran and Lockyear in 1910, as a perithelioma. More recently the term perithelioma of the uterus has been used by Green and others, to indicate a different connective tissue-like fibrotic cellular tumor, forming in the uterus. Other names applied to stromal myosis are fibromyosis, endometriosis interstitiale, stromatous endometriosis, endolymphatic stromal myosis, stromatosis, stromal sarcoma, and malignant stromatosis. The most acceptable terms of today are stromal myosis and endolymphatic stromal myosis. Over one hundred cases have been reported in the literature at the present time, and probably many others have been unrecognized.

This disease occurs from the age of twenty years upward, and some have been described after the menopause. It is not dependent for its growth on estrogenic hormone, which contrasts completely with adenomyosis.

The endometrial stroma without endometrial glands infiltrates through the myometrium. Eighty or ninety per cent of cases have been benign, while ten or twenty per cent have been malignant. There is the peculiar tendency to grow into and distend lymphatics, and to extend along the lymphatics outside the uterus into the broad ligaments. The growth may extend through the surface of the uterus onto the peritoneal surface as soft yellow nodules of endometrial-like tissue. As it extends into the parametrium and along the side walls of the pelvis, quite sizeable extraperitoneal masses of this soft, mushy and friable tissue may form, which suggests an extensive, inoperable malignancy.

Hunter (1953) has stated that there are three forms of stromal myosis. In the first, the uterus is enlarged, globular, and gives the impression of adenomyosis. The wall of the uterus suggests a "well-worn Turkish towel." The second form shows numerous polyps, of yellowish color, with smooth, bulbous surface, soft and homogenous, largely filling the endometrial cavity. In the third form, the stromal cells have reached the adnexae or peritoneum, form yellowish smooth-surfaced, ball-like masses, and the extensions into the broad ligaments have the resilience of rubber bands.

While this disease may grow into the endometrial cavity as sizeable polypoid masses, the more characteristic form is in the myometrium and parametrium, extending in the lymphatics. Worm-like ropey masses of tumor tissue may be drawn out of the lymphatics. This was pointed out in the early case of Casler (1920), and has been noted repeatedly since that time.

The fact that this disease may occur after the menopause, or may recur after removal of the ovaries or extensive irradiation therapy, indicates that it is not a form of endometriosis, and that it has an entirely different stimulus. Its most striking property is its herniation into lymph vessels.

In 1940 Goodall, in his interesting monograph on Endometriosis, presented a series of cases of stromal myosis, first bringing attention forcefully to this condition, although the picture was confusing.

The microscopic appearance, as a rule, is that of benign endometrial stroma, extending through the walls of the uterus, as does adenomyosis. In numerous areas the stroma grows into and distends the lymphatics. But a perusal of the literature shows a remarkable variation in the cases that are reported, as indicated by the published photomicrographs. Some of these suggest sarcoma, others cellular myoma, one a dysgerminoma with septa although the tumor cells were smaller; others have cords, such as occur with the arrhenoblastoma, a few have tubules and rosette-like forms, as may occur with the granulosal tumor, and a few suggest an adenocarcinoma. Evidently there are great variations in the microscopic pathology of stromal myosis, or some of these reported cases do not belong in the same category.

The symptoms are meno-metrorrhagia and pelvic pain, which are not characteristic, and examination shows enlargement of the uterus, which may be symmetrical, irregular or nodular, and there may be masses in the broad ligament or adnexal regions. Thus, there is no possible way of making a clinical diagnosis.

At the time of *operation,* the uterus is found enlarged, symmetrical or nodular, up to the size of a three months pregnancy. In the excision of the uterus, one may find the worm-like masses, growing into the lymphatics in the broad ligaments, which is a diagnostic point in the most characteristic cases. After the uterus has been excised and has been opened, often it suggests adenomyosis. With the forceps, one may pluck out the worm-like growths in the dilated lymphatics of the uterine wall. Or there may be the large, yellowish, soft polyps largely filling the uterine cavity. In other cases there may be sizeable tumor growths in the broad ligaments, or retroperitoneal regions under the ovary, or soft, yellowish nodules may occur on the surface of the uterus, ovaries or pelvic peritoneum. This appearance immediately suggests an advanced, inoperable malignancy. When biopsy is made and the final sections show benign-appearing endometrial stroma, or in the rare instance a malignant appearance, with irregularity of the cells, mitosis, and some previously described variations which may make the diagnosis difficult, the best procedure is extensive surgery, attempting to dissect out all of the retroperitoneal growth. Excision of all of the tumor is the best attack, because, as a rule, the growth is not susceptible to irradiation therapy.

Regardless of treatment, recurrence may follow in a few months, a few years, or many years. Repeated excision may be attempted.

As a rule, the disease is benign, with a tendency to local recurrence.

The relation of this strange disease to endometriosis is uncertain, but it is evidently different. Endometriosis is related in its growth directly to estrogenic hormone, whereas the disease of stromal myosis has an entirely different source of impetus.

INDICATIONS FOR HYSTERECTOMY

Because it is difficult to find in a text-book the various indications for hysterectomy, as the reasons are scattered throughout its many pages, and because definite opinions are not too clearly expressed, this important clinical aspect of gynecology will be discussed briefly in this section.

When the health of a woman, physically and emotionally, is compromised by an abnormal uterus to a serious degree, excision has proved to be one of the most satisfactory procedures of all surgical operations. Hysterectomy should never be performed for minor complaints and minor findings, but only when there are major diseases, or when the complaints and findings add up to a major disability.

For a century, perhaps for many centuries, nervous complaints have been attributed to the menopause (at any age whatever, whether the patient is menstruating or not), or to certain minor or major physical abnormalities, which may be present in the pelvis. It is only after accurate observation and examination have indicated precisely which symptoms are caused by the specific findings in the pelvis, that one can expect relief from symptoms by correction of the pathological conditions present. Every surgeon must beware of attempting to cure symptoms that cannot possibly be caused by abnormality in the pelvic organs. When operations are mistakenly performed for anxiety states, nervous exhaustion, overwork, tension or headaches, often the patients are not helped, and further deterioration may follow. One of the greatest pitfall is the performance of surgery for severe or marked pain when there is no demonstrable pathology. After study and observation, occasionally one may decide that exploratory operation is necessary. A few patients may be cured by this procedure, even though no obvious explanation for the pain is discovered, but more are not cured, and tend to develop various other complaints.

The indications for hysterectomy have been broadened from thirty years ago, when only very large tumors, extensive inflammatory disease, or obvious invasive cancers, were considered suitable for surgical operation, probably because of the greater morbidity and mortality then. In the past ten or fifteen years, abdominal total hysterectomy has superseded subtotal hysterectomy, because of the incidence of carcinoma subsequently developing in the cervical stump, and because of the frequent chronic infection in the retained cervix. The mortality rate from total hysterectomy has dropped from six or seven per cent to three per cent, to one per cent, and now to about two-tenths of one per cent. Another great change that has occurred in the past ten or fifteen years is the rising popularity of vaginal hysterectomy. This latter procedure has obviated the abdominal incision and has emphasized and aided the repair of cystocele, rectocele and enterocele.

In the past, and at the present time, *myoma* of the uterus is the most frequent indication for abdominal hysterectomy, making up 30.5 per cent of our cases. Of this group, one-half were operated on because of the *large* size of the tumor, one-third because of *pain* from the tumors, and one-sixth because of *hemorrhage*.

It is considered that any uterus larger than a three month's pregnancy should be excised. Exceptions are poor risks, psychological inability to accept the operation, or preference to have the tumor observed. Many of those removed for large size have degrees of abnormal bleeding and abdominal discomfort, but the prime reason in this fifteen per cent of the total is the size.

In one-third of the myoma cases, pain was sufficiently marked, from pressure against the lateral wall of the pelvis, from extension beneath the bladder, or pressure against other pelvic viscera, to cause the patient to seek relief from the pain. Not always is the pain relieved by hysterectomy, but in the majority of those carefully studied, the result is very satisfactory. In one-sixth of the myoma cases, menorrhagia and metrorrhagia, usually severe enough to cause degrees of secondary anemia, and its attendant symptoms of weakness or exhaustion, were prominent reasons for hysterectomy.

Adenocarcinoma of the endometrium is a second reason for hysterectomy, making up five and five-tenths per cent of abdominal total hysterectomies. Surgical excision, including the tubes and ovaries, is the prime treatment in this disease. Radical hysterectomy, with removal of pelvic lymph nodes, is preferable, but as a rule, age of the patient, obesity, and medical complications, prevent extensive surgery in this particular group. The majority opinion today favors preoperative radium therapy, though some surgeons feel that irradiation therapy does not improve the final results.

Salpingitis was a reason for hysterectomy in eight and six-tenths per cent of cases. Persistent symptoms and palpable masses from chronic pelvic inflammatory disease, not responding to antibiotic therapy, douches and rest, are indications for operation. As a general rule, when the fallopian tubes must be removed, also the uterus should be excised. Uteri that are retained after bilateral salpingectomy, are prone to develop functional disturbances, may form the various neoplastic diseases in later life, and may cause pain from displacements and adhesions. Occasionally, in young women, it may be advantageous psychologically not to remove the uterus after bilateral salpingectomy, even though subsequently hysterectomy may be necessary in later years. In a few, the psychology of menstruation is important.

Of the group with salpingitis, six and six-tenths per cent were of tubercular origin. Some of these may be diagnosed before excision, and may be treated medically (though the results are indefinite), but the pathologist finds the true etiology in the majority.

Abdominal pain has persisted in thirteen and six-tenths per cent of our patients operated on for salpingitis, which gives credence to the adage, "a surgeon will not make a reputation operating for salpingitis." For this reason, the medical treatment should be used thoroughly before laparotomy.

For *ovarian tumor,* laparotomy and hysterectomy were performed in three and six-tenths per cent of cases, and one and five-tenths per cent were for carcinoma of the ovary. In the benign cases, there was concomitant uterine disease. Malignant disease of the ovary always requires a complete operation, if possible.

Endometriosis of severe degree required a complete operation, including hysterectomy, in eleven and four-tenths per cent of the abdominal hysterectomy cases. Myomas and cervicitis occurred in over half of these cases, adenomyosis of the uterus in one-fourth, and retroversion in one-fourth. Actually, many more cases with hysterectomy had some degrees of endometriosis, but in those, it was not the primary reason for operation. When surgery is necessary for endometriosis, in a large percentage (forty per cent of those operated upon), a conservative operation, retaining the childbearing function, is performed.

Carcinoma of the cervix, in three and five-tenths per cent of our cases of hysterectomy, has been treated with radical total hysterectomy and pelvic node dissection. A majority feel that irradiation therapy alone should be used for carcinoma of the cervix, some prefer radical surgery alone, and a few prefer irradiation therapy, followed by wide excision of the pelvic tissues, including pelvic node dissection. In our experience, the latter method seems better and is used for Clinical Stage I lesions. Irradiation therapy alone is used in the cases with extension beyond the cervix. Carcinoma-in-situ lesions in older women are treated by total hysterectomy, in young women by excision of a cone of tissue. The latter are followed carefully by repeated Papanicolaou cytology studies.

The next group is a large one, approximating the same number as the myoma group (thirty and five-tenths per cent), encompassing multiple smaller lesions and positive distressing symptoms, which we have termed a *"combined syndrome."* This is a combination of multiple organic abnormalities, none alone sufficiently important to require operation, associated with multiple positive and distressing symptoms, which summate to a major disability. Vaginal outlet relaxation, cystocele, rectocele, enterocele, descensus of the uterus of first or second degree, hypertrophy and lacerations of the cervix, retroversion of the uterus, "general pelvic relaxation" with associated enlarged pelvic veins, "pelvic congestion," and the "congestion fibrosis syndrome," may be placed together, and may form one basic part of the syndrome. Chronic cervicitis and small myomas are frequently present, but of themselves not sufficient for hysterectomy. But the small myomas add to the dysfunction, weight and prolapse of the uterus, and

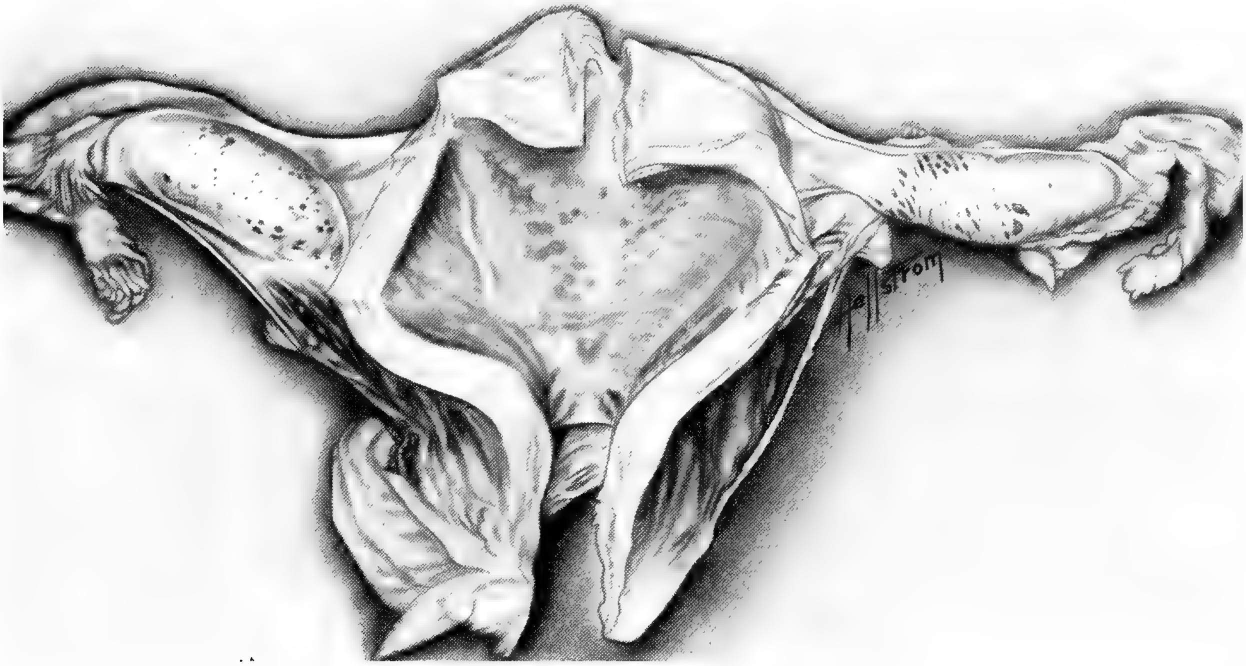

Fig. 155. Stricture of the cervix with pyometrium. A post-menopausal woman with symptoms of pelvic pain, tenderness and fever. Drainage through the vagina is preferable to hysterectomy. Carcinoma of the endocervix or endometrium commonly is associated. Note atrophic ovaries. Sometimes mucus may accumulate in the endometrial cavity after estrogenic hormone is given post-menopausally.

are additive factors in these particular cases. Subinvolution of the uterus was recorded by the pathologist in one-fourth of the cases, and salpingitis in one-seventh. Mild degrees of endometriosis was found in one-third of these cases. Smaller ovarian cysts, dermoid, serous, or endometrial, may be present. Post-operative adhesions, menorrhagia, metrorrhagia, dysmenorrhea in later life, and dyspareunia, are commonly present. Bearing down pressure pain and heaviness are characteristic symptoms.

But in these cases, where these multiple small pathological findings may be present, they alone are not sufficient to necessitate hysterectomy. Only when these are associated directly with positive and distressing symptoms does the real indication for operation exist. Often the hysterectomy is only a part of the operation, as the restoration of pelvic support may be most important.

Menometrorrhagia, not responding to curettage and medical therapy, was an indication for hysterectomy in three and five-tenths per cent of cases. As a rule, these patients were menopausal or near the menopause. Irradiation therapy formerly was used in this group, but it is not to be preferred, except when patients fear operation intensely, or have medical disease prohibiting hysterectomy.

Pregnancy complications have been a reason for hysterectomy in eight-tenths per cent of cases. This included cornual pregnancy, old tubal pregnancy with opposite tube absent, hysterectomy for sterilization in patients with tuberculosis and psychiatric disease, recurrent hydatid mole, and chorioma destruens.

Rare indications for hysterectomy have made up a total of one per cent of our cases. These include sarcoma of the uterus (with pre-operative diagnosis), cervical stricture, severe chronic cervicitis, pelvic adhesions, and symptomatic retroversion near the menopause.

VAGINAL HYSTERECTOMY

Vaginal hysterectomy is being performed much more widely in the past few years. In some centers, from fifty to seventy-five per cent of all hysterectomies are performed by the vaginal approach. In our own experience, thirty per cent are vaginal hysterectomies. The indications for vaginal hysterectomy may be divided into three groups. *Third degree prolapse* with cystocele and rectocele formerly was treated by the Manchester-Fothergill procedure of amputating the cervix and performing cystocele and rectocele repair, by the Watkin's interposition operation of placing the corpus of the uterus beneath the bladder for support, and by the LeFort vaginal obliteration operation. Now, as a rule, vaginal hysterectomy, with cystocele and rectocele repair, is preferred for third degree prolapse. The second and largest group encompasses *first and second degree prolapse* with vaginal relaxation, and usually with multiple minor diseases of the uterus, associated with positive symptoms. In this category is included particularly the "combined syndrome." Removal of the uterus with second degree prolapse does facilitate the repair, but as a rule, the uterus is removed purposely for disease. The third, and smallest group, is made up of cases with *multiple small uterine lesions,* without prolapse, cystocele and rectocele. This includes menorrhagia and metrorrhagia near the menopause, after malignancy has been excluded, and not responding to simpler treatment, often with chronic cervicitis, small myomas, subinvolution and retroversion.

There are more post-operative complications in the group in which vaginal hysterectomy is performed, particularly urinary tract difficulties. The commonest is delayed voiding in those with extensive cystocele repair.

SYMPTOMS, DIFFICULTIES AND RESULTS IN RELATION TO HYSTERECTOMY

The indications for hysterectomy include these features: positive symptoms and positive findings, in a patient who has been partially or wholly incapacitated, who understands what the procedure will do, who has not been unduly urged, who has thought the matter over carefully, and who wants the operation.

There are many pitfalls in this operation. The risks are slight, but should not be minimized to the patient. The despairing hope of an unhappy woman that hysterectomy might cure her nervousness must be constantly searched for and clarified. Rarely does hysterectomy cure nervousness, unless it is caused by pain, fear of fatal hemorrhage, knowledge of a lesion suggestive of malignancy, or occasionally, extreme fear of pregnancy.

The concern that the performance of hysterectomy for metrorrhagia in late menstrual life will lead to too many operations does not change our belief that if such bleeding does not respond to curettage, thyroid therapy and psychosomatic advice, hysterectomy usually is preferable to radium or roentgen castration.

A serious objection to the ultraconservative attitude is the risk of overlooking a malignant process. Not only must all patients with erosion of the cervix have Papanicolaou smears or biopsy, except in the very young, and all with irregular bleeding have curettage, except puberty bleeders, but great care must be exercised in differentiating pelvic tumors. A benign myoma must not be confused with ovarian carcinoma.

In our experience, eight and seven-tenths per cent of cases with hysterectomy had a preoperative diagnosis of malignancy, including those of the endometrium, cervix and ovary. In addition, there were one and eight-tenths per cent of unexpected malignant processes found in the excised tissue. Thus, a total of ten and five-tenths per cent of cases with hysterectomy had a malignant growth.

A varying percentage of patients are nervous after their hysterectomy, but most of these were nervous before the operation. Unfortunately, many hope they will never be nervous again. It is so easy for the patient to forget the preoperative explanation and think she has found a cure of family troubles. The functional element is an important factor in every branch of medicine and surgery; certainly it is prominent in pelvic surgery. Analysis of our patients has shown that fourteen per cent of the benign group (one expects those with malignancies to have degrees of anxiety) had functional postoperative nervous complaints. Study has indicated that these complaints were not related to the operation or menopause in most instances. In four and eight-tenths per cent of our cases with benign disease, the patients complained of some degree of postoperative abdominal pain.

It is for the group with "combined syndrome," multiple pelvic lesions with symptoms adding up to a major disability, that most accurate clinical judgement must be exercised. Decision should not be made until the patient has been interviewed several times, until all domestic factors have been taken into consideration, and until the patient understands clearly the reasons for hysterectomy and the results to be expected. Patients with only functional nervous complaints are not suitable candidates for hysterectomy.

SUMMARY OF INDICATIONS FOR HYSTERECTOMY

Cases for hysterectomy may be divided into two groups: those in which hysterectomy is relatively imperative and in which the indications are obvious, and those in which hysterectomy may be delated for study and convenience.

The first group, in which hysterectomy is imperative, includes those with large tumors, painful myomas from pressure, hemorrhaging myomas with anemia, malignancies of the uterus, ovarian tumors, severe endometriosis and severe pelvic inflammatory disease. This includes permanent pelvic masses, and commonly requires surgery, regardless of symptoms. These totaled fifty-two per cent of our patients.

The second group includes those in which hysterectomy may be delayed, and comprise many of the cases with "combined syndrome," with multiple positive findings, each relatively minor in itself, and positive symptoms, which summate to a major disability. These have composed forty-eight per cent of our cases, in which the hysterectomy may have been delayed for convenience of a domestic state, but which was necessary just the same for the best health of the patient. In this group, the operation is partly elective and can be postponed for a limited period of time.

Malignant disease, both with preoperative diagnosis and that found by the pathologist after hysterectomy, is an important factor in pelvic surgery, and occurred in ten and five-tenths per cent of our cases with hysterectomy.

If care is taken in the selection of cases for hysterectomy, the results in the great majority are most satisfactory.

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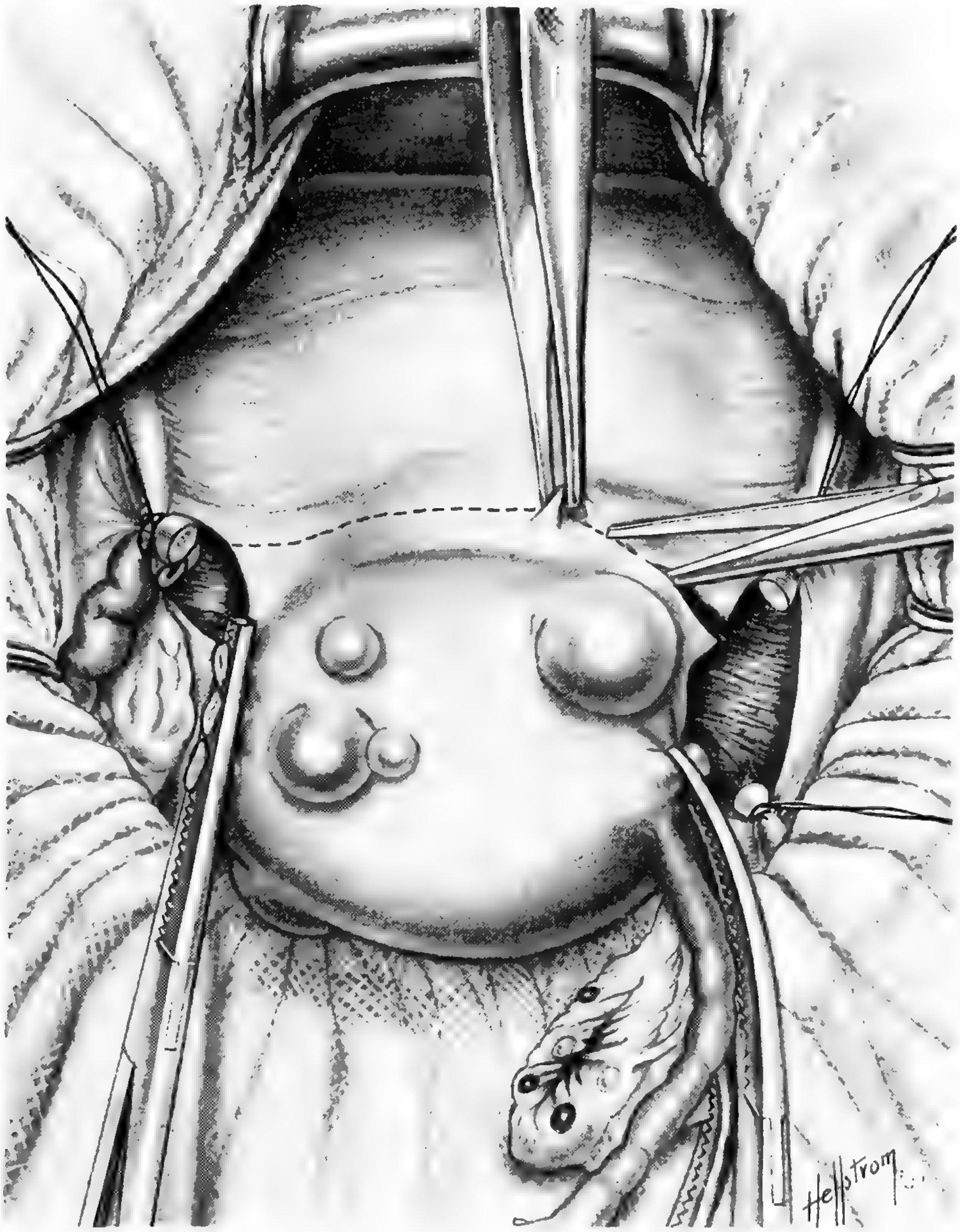

Fig. 156. Abdominal total hysterectomy technique. Left tube, utero-ovarian and round ligaments divided and doubly ligated; right round ligament and ovarian ligament ligated and divided; bladder peritoneum mobilized.

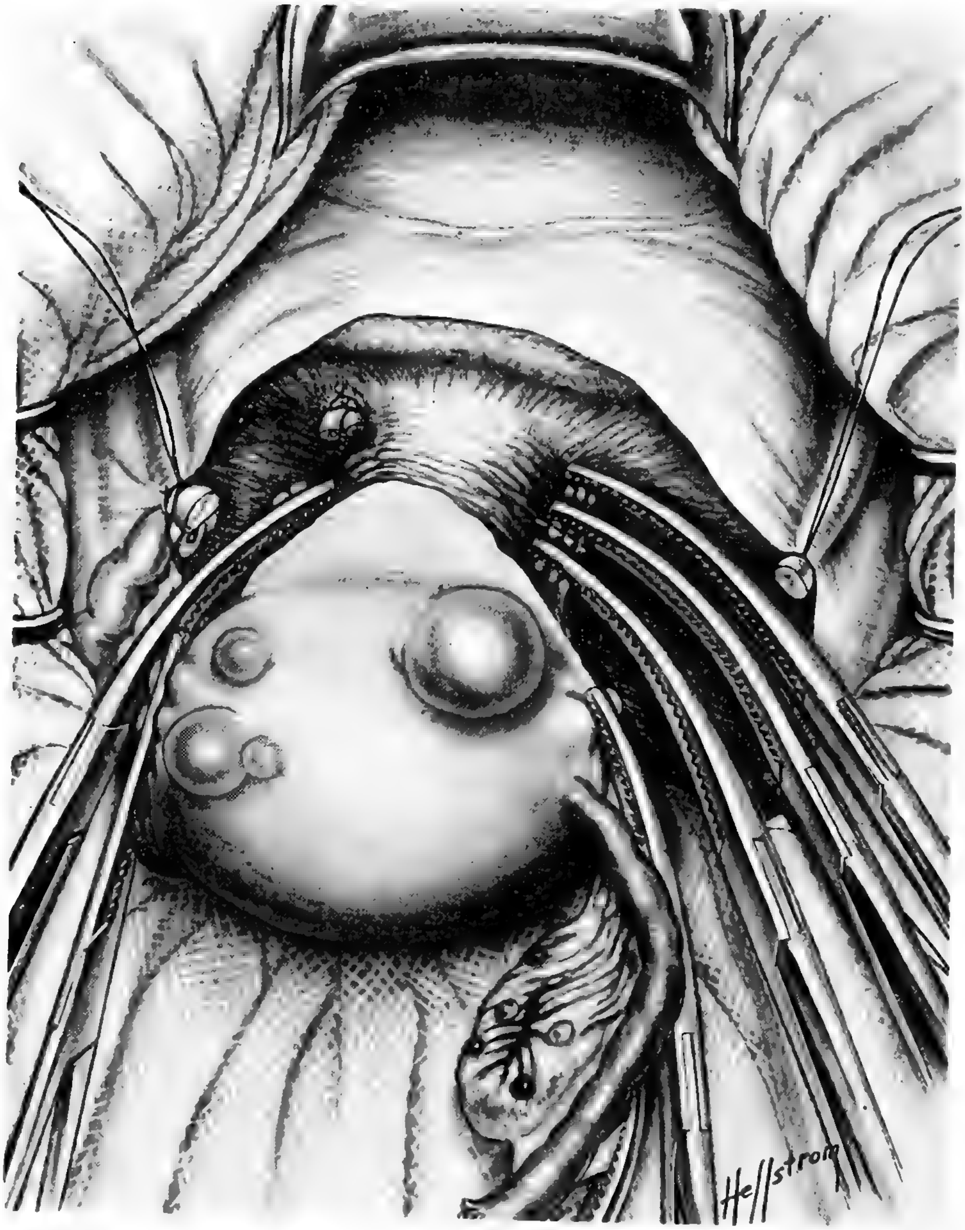

Fig. 157. Uterine vessels isolated, triply clamped, cut and doubly ligated.

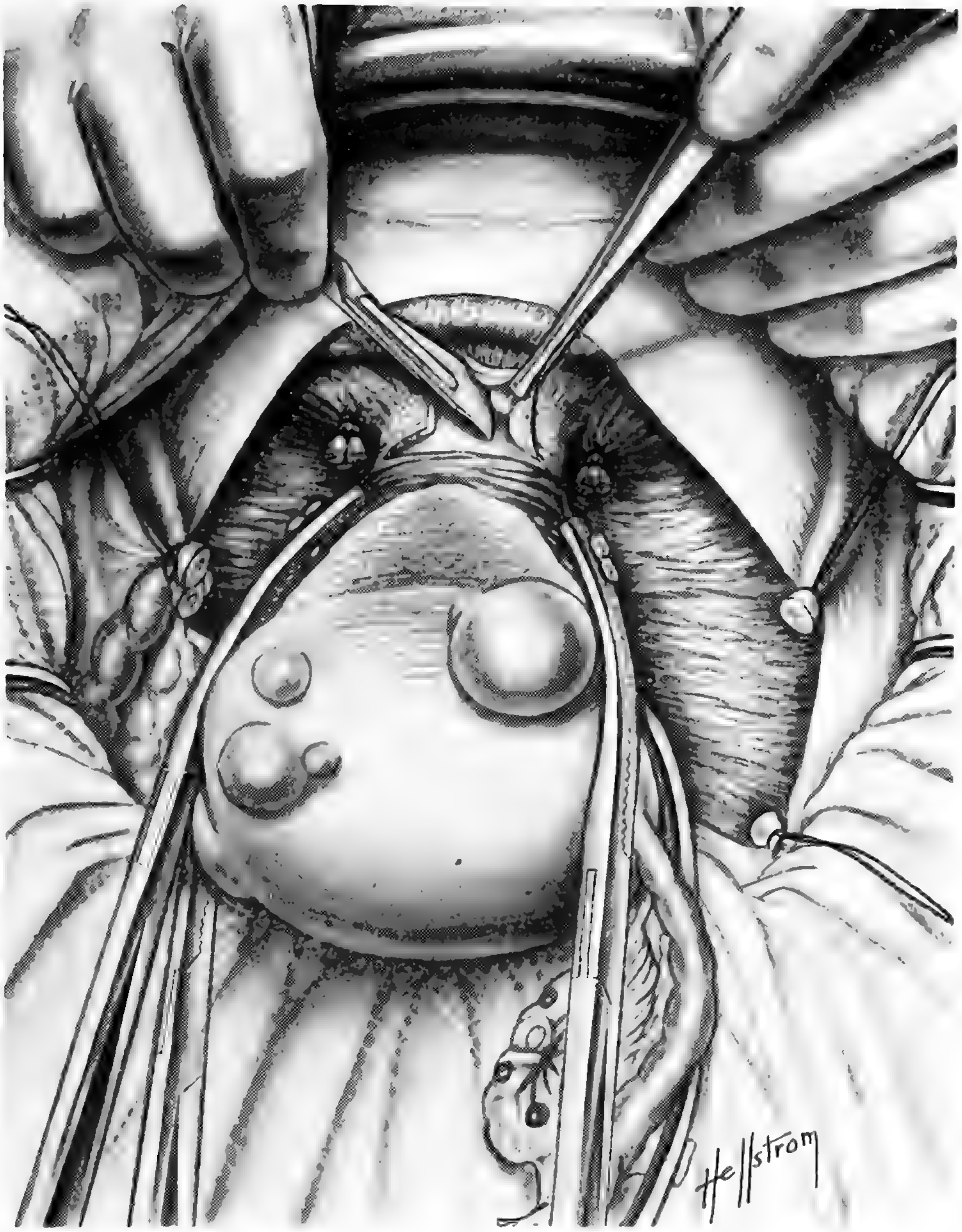

Fig. 158. Richardson's "T" incision in pubocervical fascia.

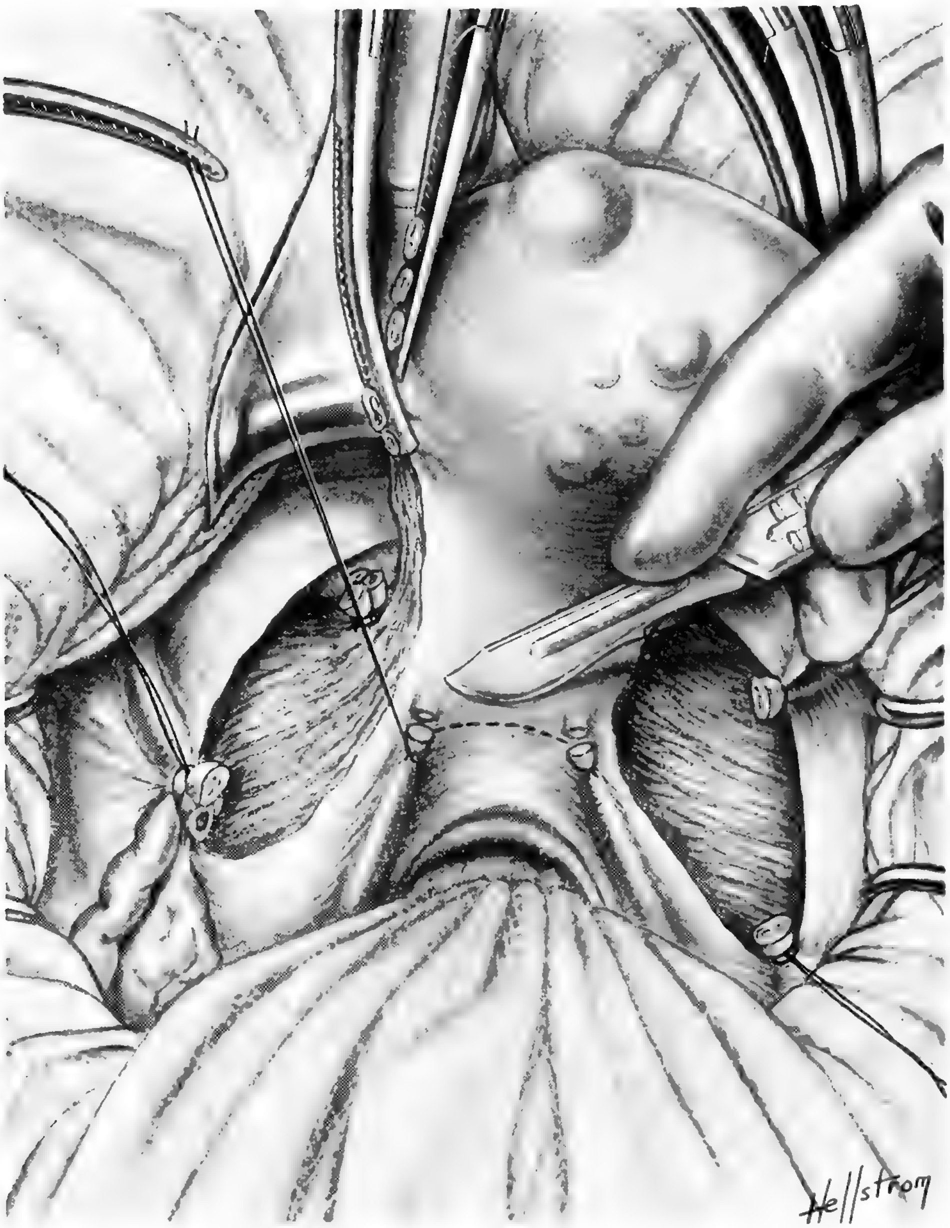

Fig. 159. Uterosacral ligaments clamped, ligated and divided.

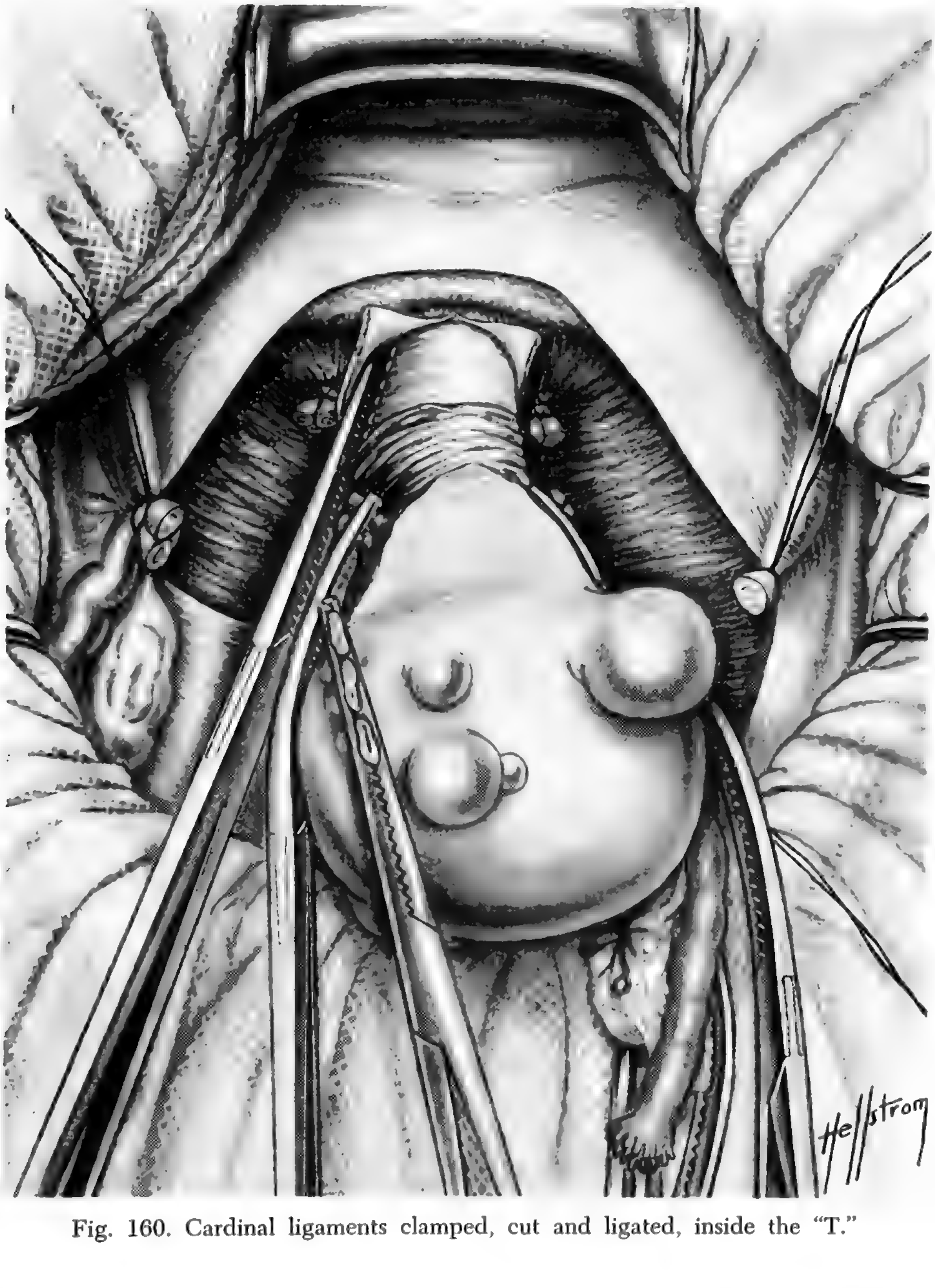

Fig. 160. Cardinal ligaments clamped, cut and ligated, inside the "T."

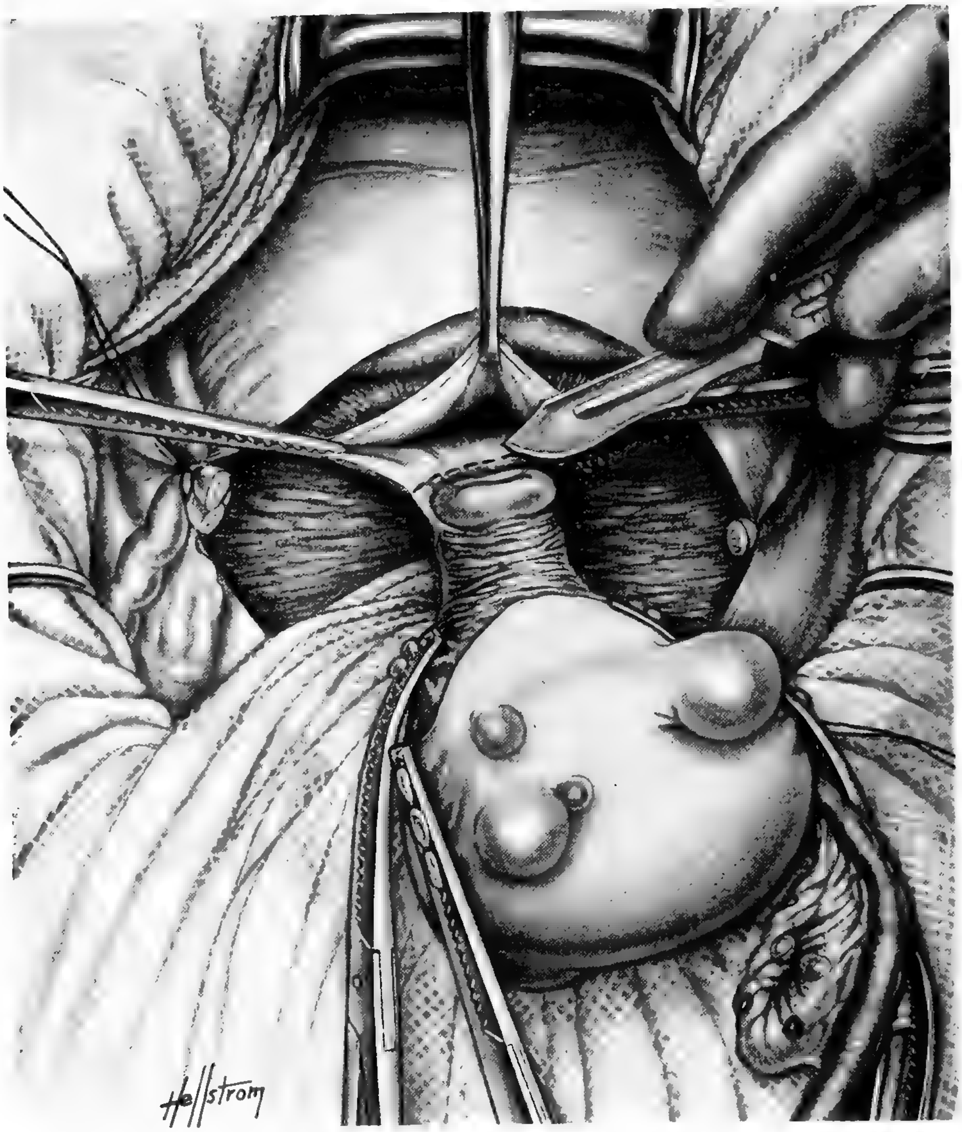

Fig. 161. Cervix excised from vagina. One clamp anterior, posterior and at each lateral angle.

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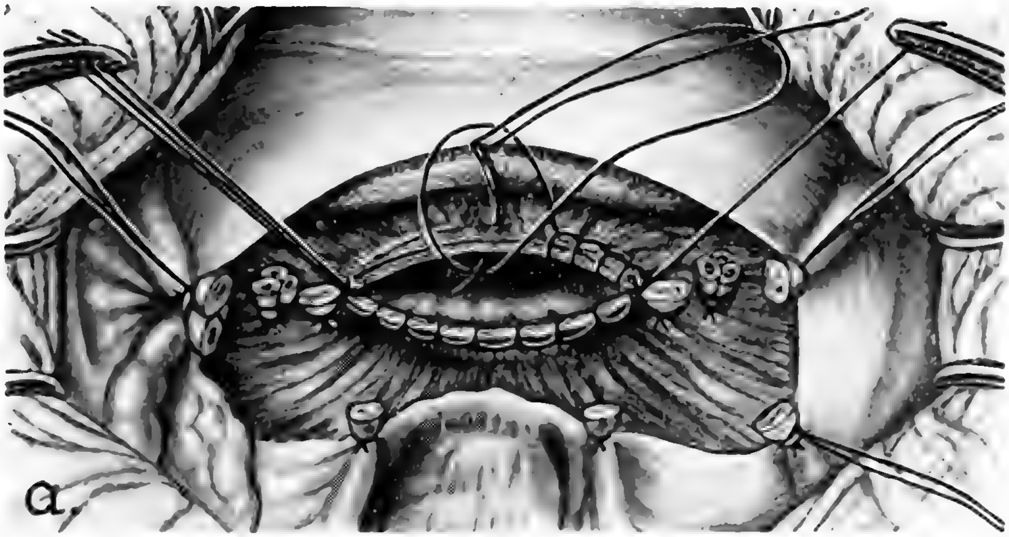
Fig. 162. a. A lock-stitch of chromic suture is placed around the vagina.

b. The angles are partially closed with figure-of-eight sutures.

c. Uterosacral and cardinal ligaments are sutured to the angles.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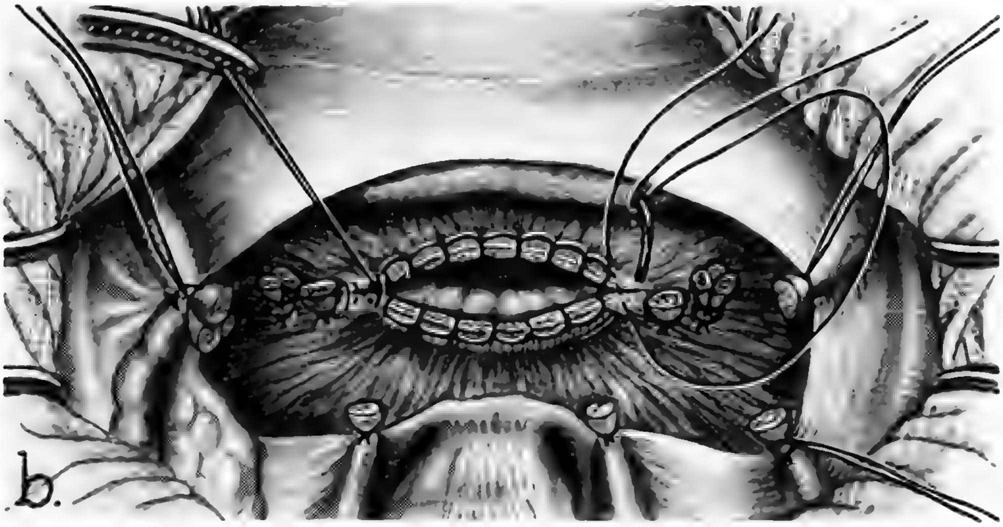
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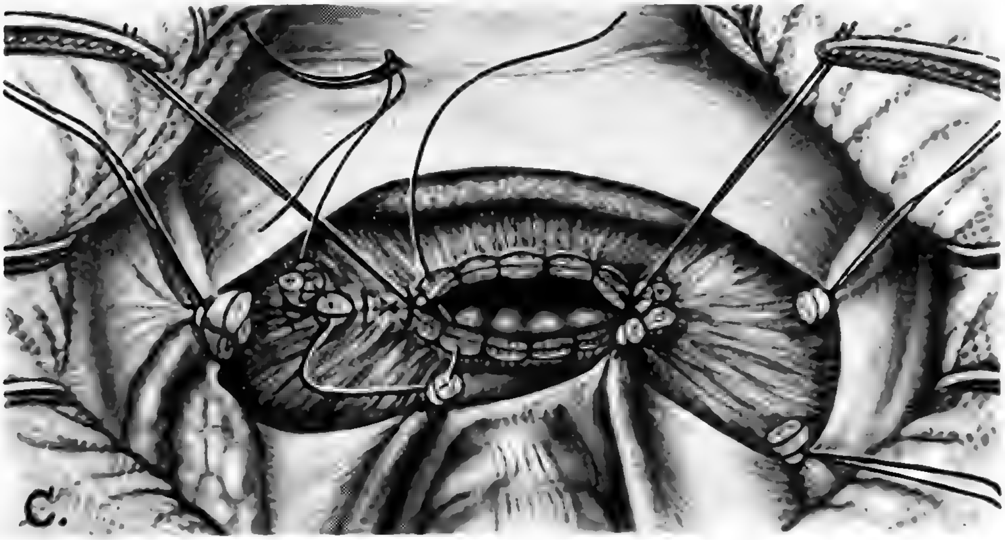
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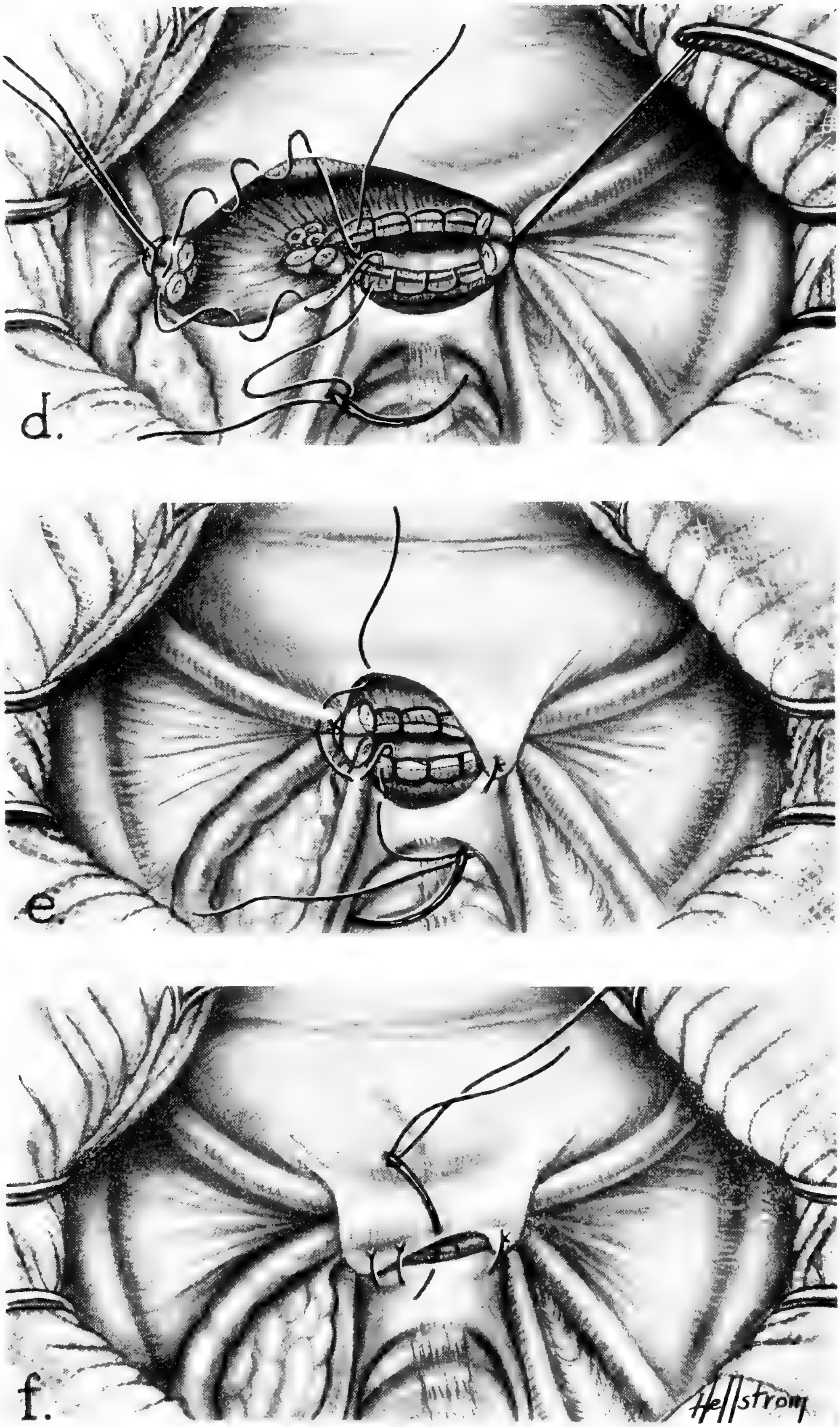
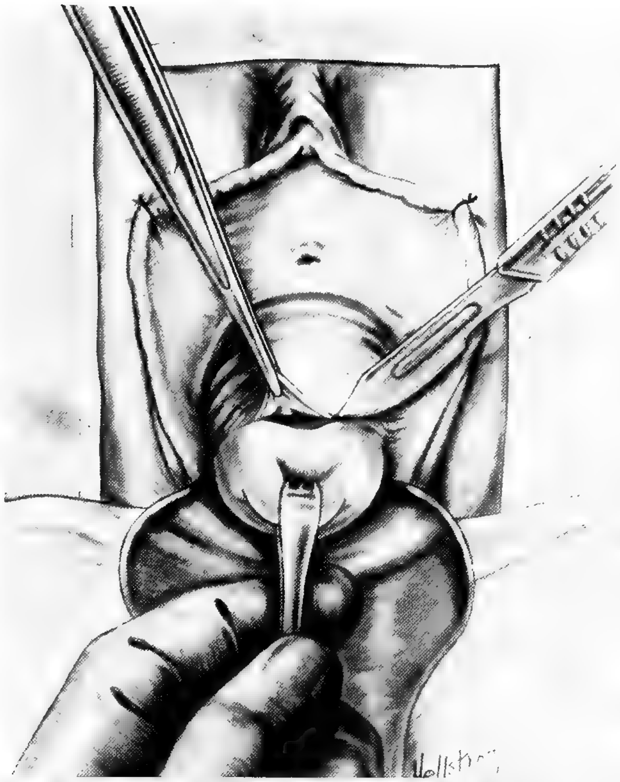
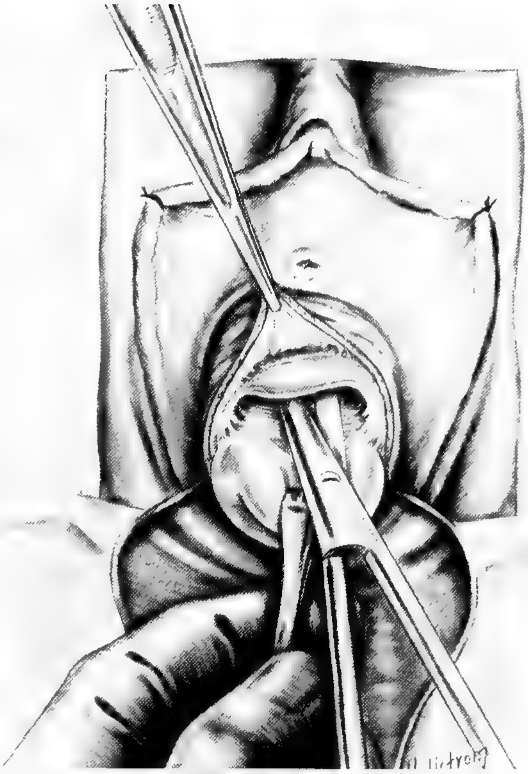
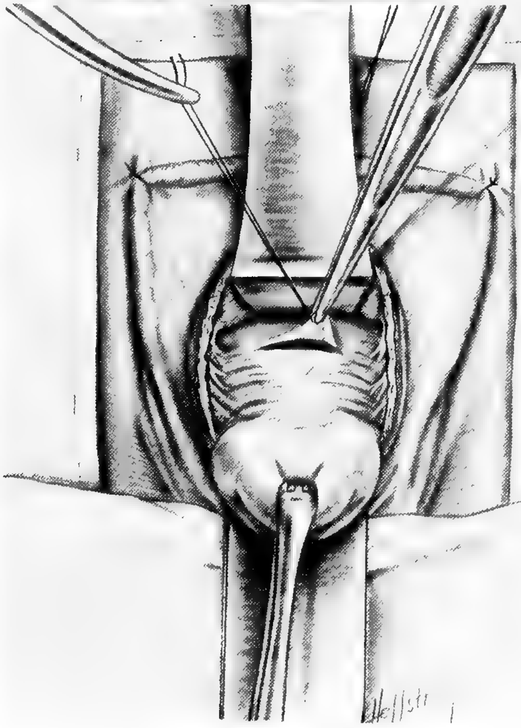


Fig. 163. d. The "pulley" suture reefs the broad ligament and attaches pedicle to vagina.
e. Bladder peritoneum and round ligament are sutured to posterior vagina.
f. Fine sutures attach bladder peritoneum to posterior cul-de-sac.







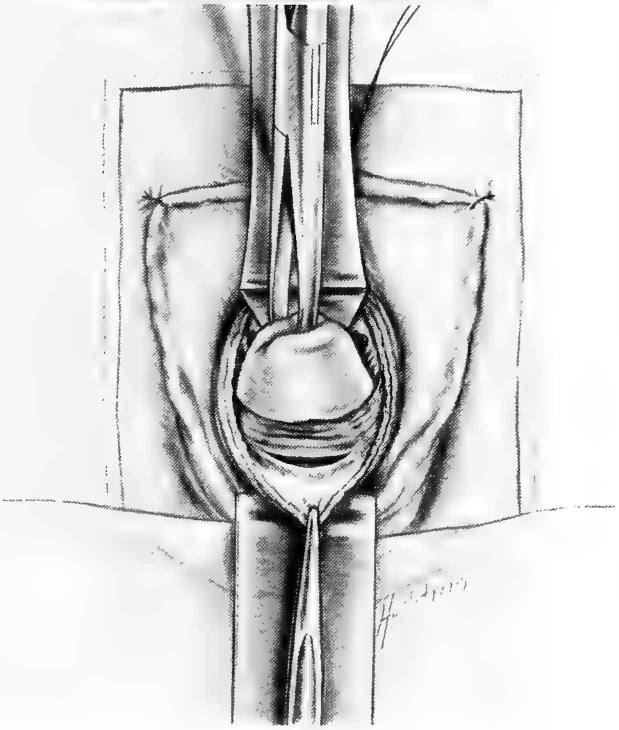
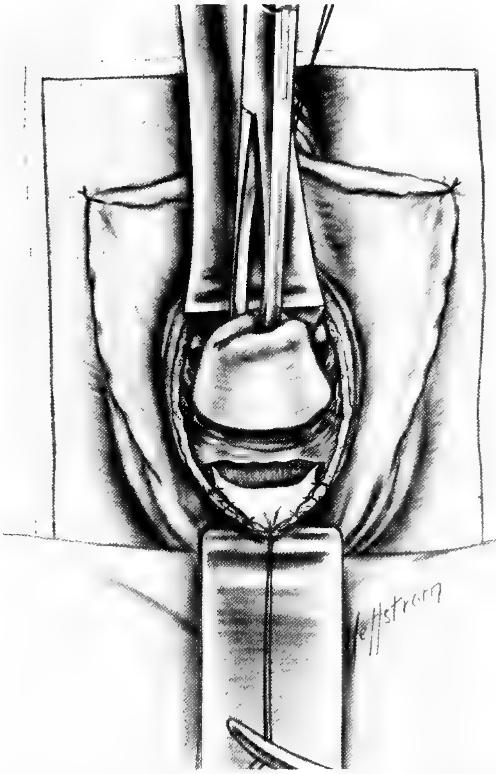


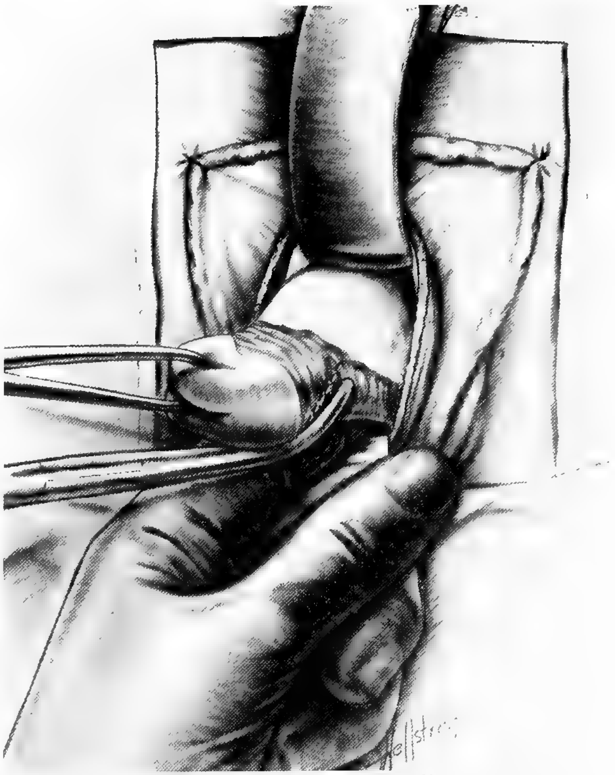
Fig. 164. Vaginal hysterectomy technique. Incision in the vagina will encircle the cervix, reasonably low to avoid injury to the bladder.

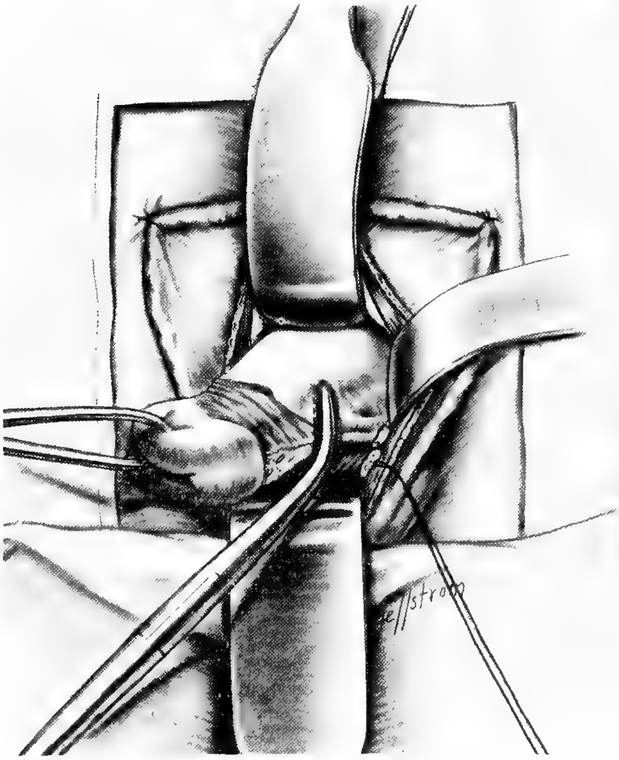
Fig. 165. The bladder is separated from the cervix by sharp scissor dissection until the loose tissue beneath the peritoneal reflection is reached. The pillars are not cut on each side, for fear of injuring the ureters, but clamps are later placed medially.

Fig. 166. The bladder reflection of peritoneum is entered, tagged for later identification, and opened to each side. The short right angle retractor will be removed and the long curved Heaney retractor inserted beneath the bladder into the peritoneal cavity.

Fig. 167. The cervix is elevated and the posterior cul-de-sac is entered.







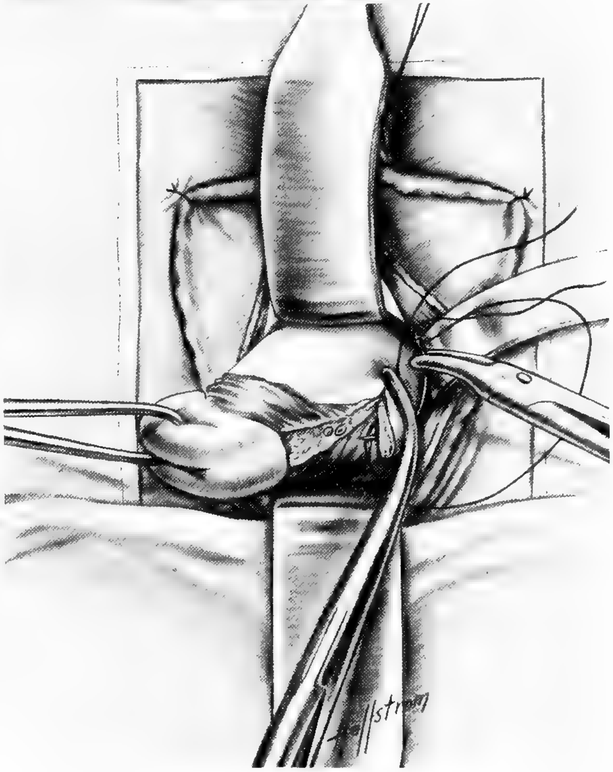


Fig. 168. The posterior cul-de-sac peritoneum is sutured to the vagina to control oozing; the second long curved Heaney retractor will be inserted posteriorly into the peritoneal cavity.

Fig. 169. The uterosacral ligament is clamped, divided, ligated and tagged.

Fig. 170. The uterine vessels are clamped, after separate division of the uterosacral and cardinal ligaments. (The lateral retractor would be better placed outside the vaginal cuff, to avoid injury to the vessels).

Fig. 171. The uterine vessels usually are ligated doubly, with transfixion sutures. Number one chromic catgut is used, as one proceeds up the sides of the uterus.

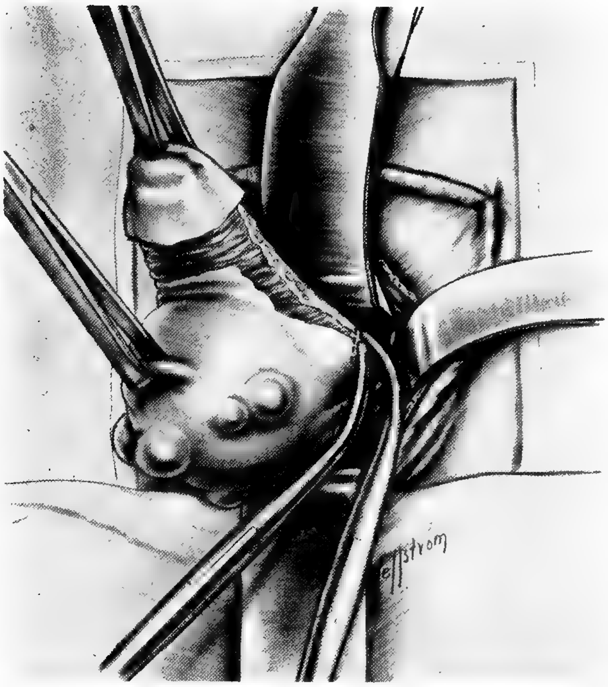


Fig. 172. The corpus commonly is delivered posteriorly, the tubes, utero-ovarian, and round ligaments are doubly clamped, and the specimen is cut away. This pedicle is also doubly sutured.

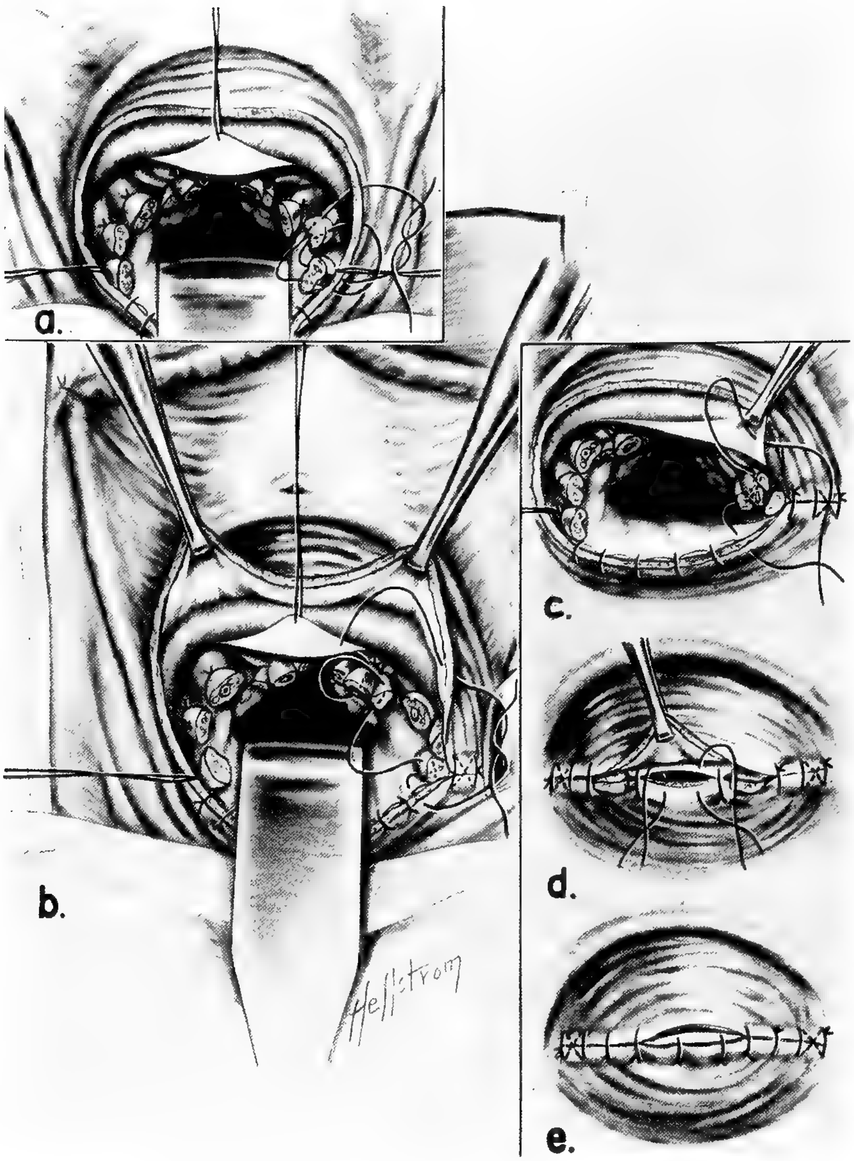


Fig. 173. Closure of vaginal hysterectomy.

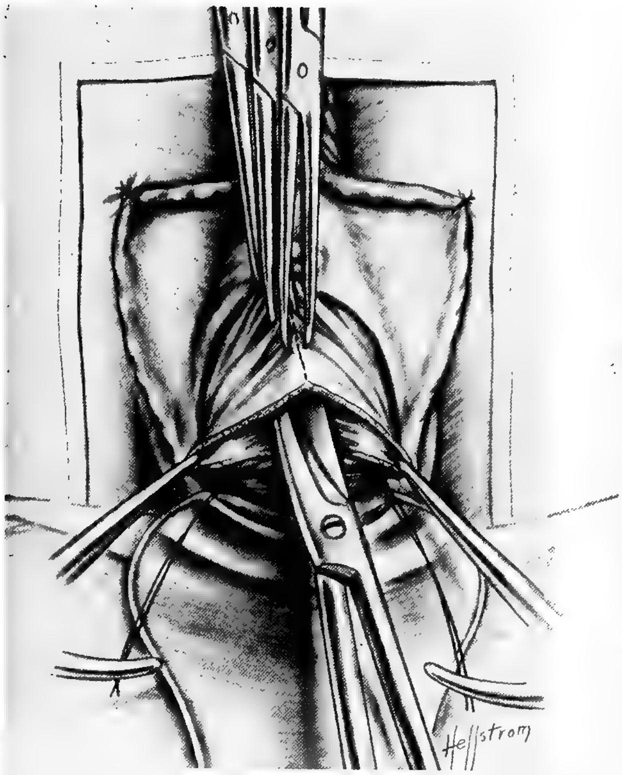
(a) The "petite" angle suture, a figure-of-eight, attaches the cardinal and uterosacral ligaments to the angle of the vagina.

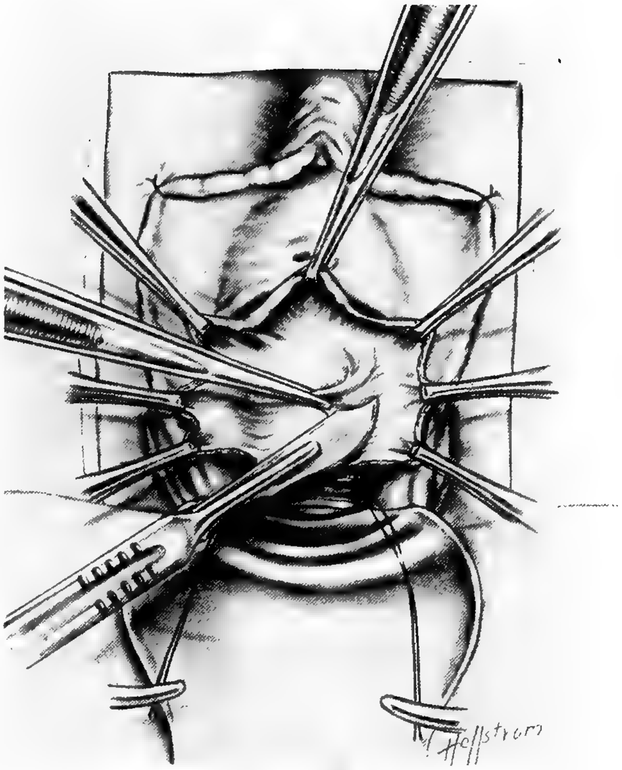
(b) The "grande" angle suture draws the anterior bladder peritoneum, tube, utero-ovarian and round ligament to the uterosacral and anterior and posterior vaginal walls. The "Heaney" angle closure omitted the first figure-of-eight, but in addition reefed the posterior broad ligament and looped around the uterine vessels.

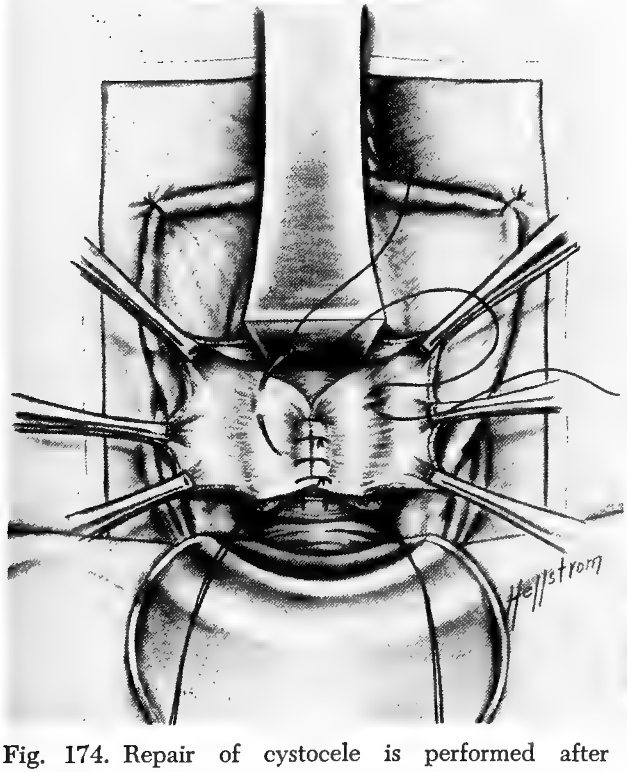
(c) A "medial" angle suture attaches the bladder peritoneum and stumps of the tube, round and utero-ovarian ligaments to the posterior peritoneum and posterior vaginal wall, further everting the ligaments. This does not include the anterior vaginal wall.

(d) The bladder peritoneum is sutured to the posterior cul-de-sac peritoneum and posterior vaginal wall.

(e) Completed operation, if no repair is to be done. Note the opening into the retrovesical space, which should at least admit one finger, (extraperitoneal drainage without a drain). This method is almost the identical reverse of our present technique for abdominal hysterectomy.







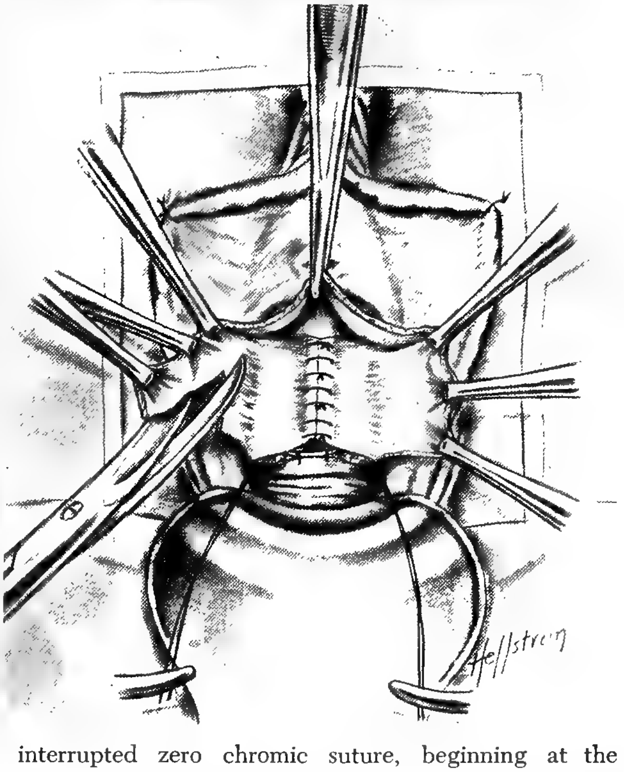
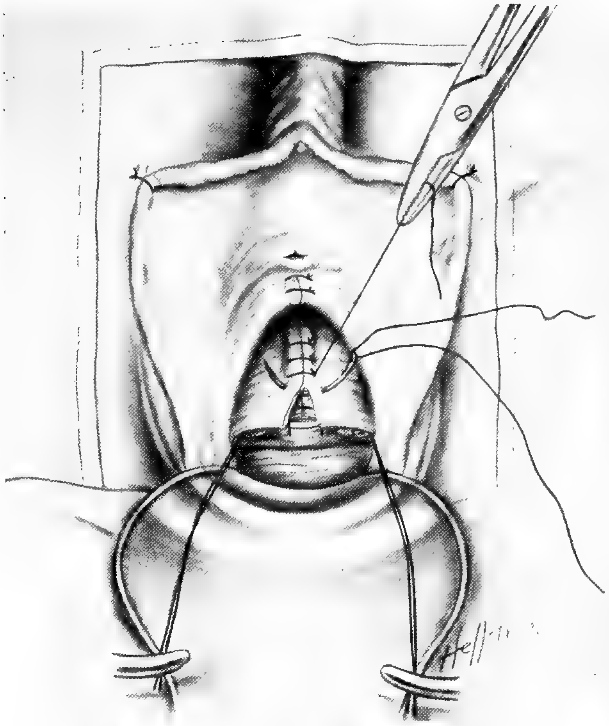


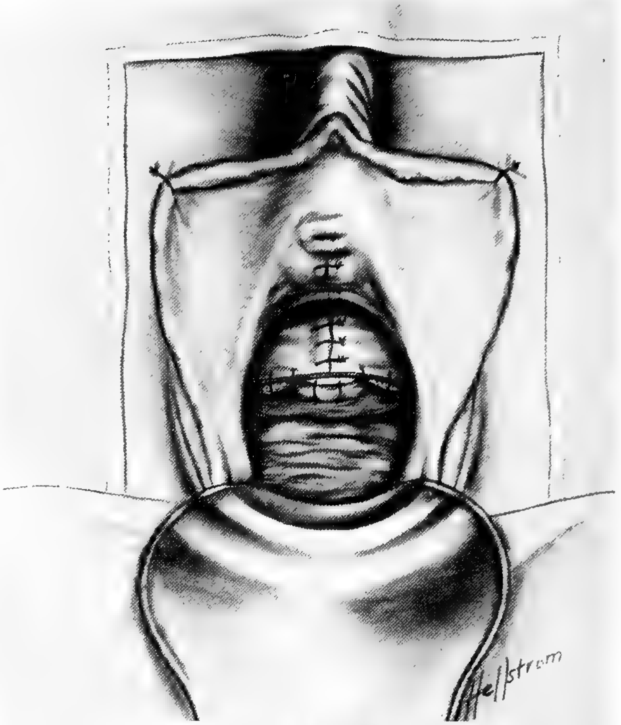
Fig. 174. Repair of cystocele is performed after inserting the angle sutures and attaching the bladder peritoneum to the cul-de-sac, closing the peritoneal cavity. The curved scissors are inserted and opened, then the vaginal wall is incised.

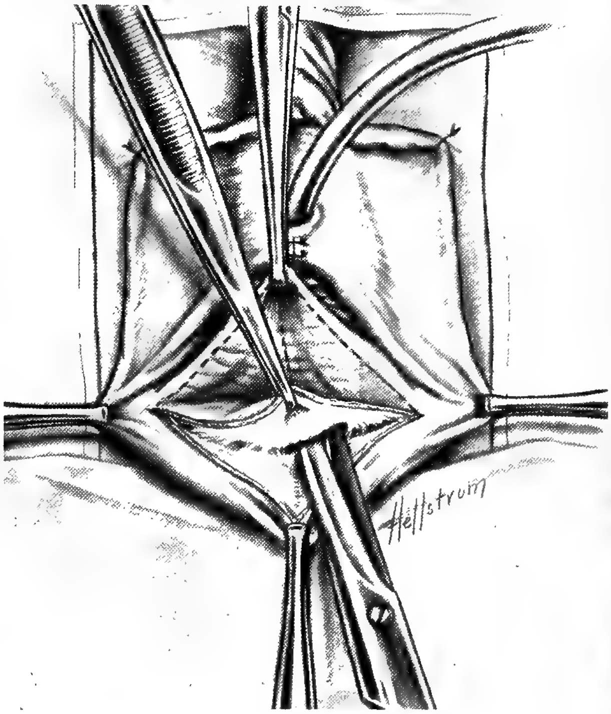
Fig. 175. The pubocervical fascia is separated from the anterior vaginal wall, using sharp dissection, often with one finger behind the reflected vaginal mucosa.

Fig. 176. The pubocervical fascia is plicated with interrupted zero chromic suture, beginning at the apex of the vagina. Care should be taken to raise the level of the internal sphincter of the bladder, in order to insure a proper posterior angle between the line of the urethra and the floor of the bladder, an apparent necessity for urinary continence.

Fig. 177. A limited amount of vaginal mucosa is trimmed away, in order not to narrow the upper vagina.







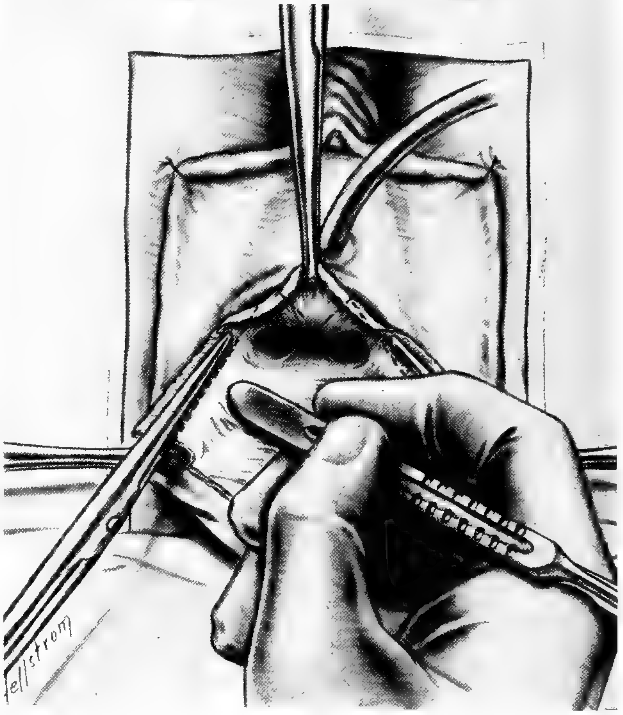
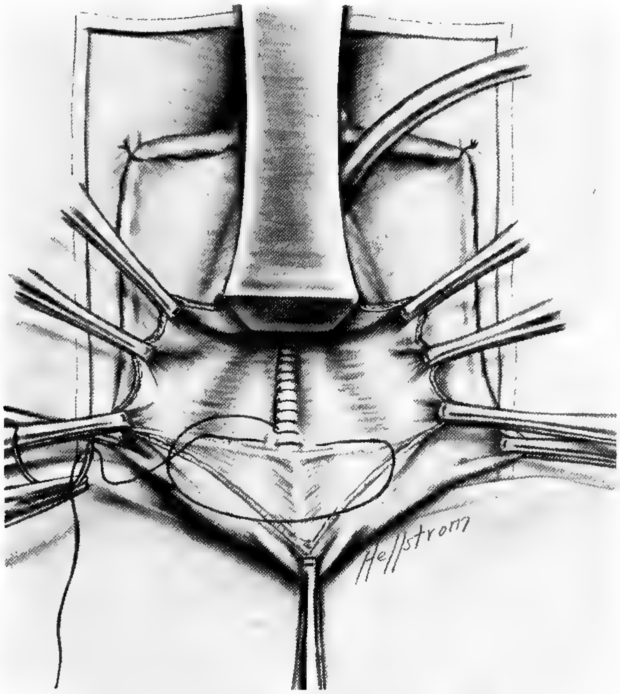


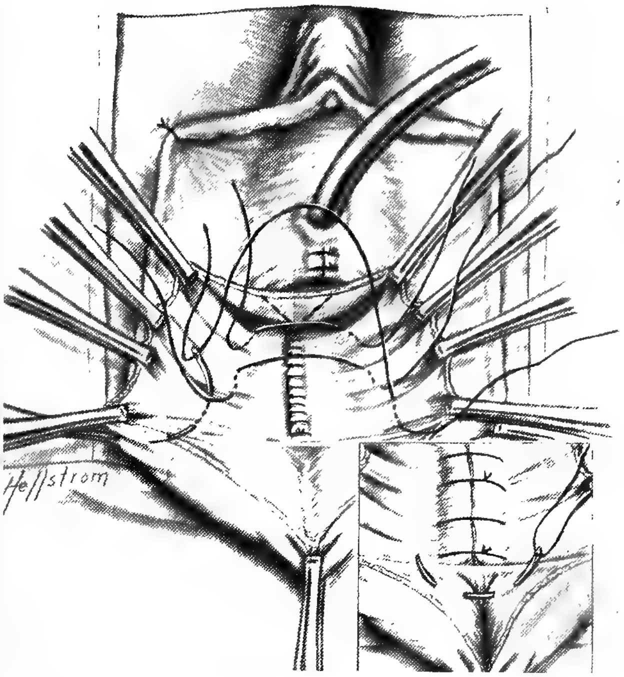
Fig. 178. Closure of the anterior vaginal wall is with interrupted suture, zero or double zero chromic, attaching to the plicated pubocervical fascia.

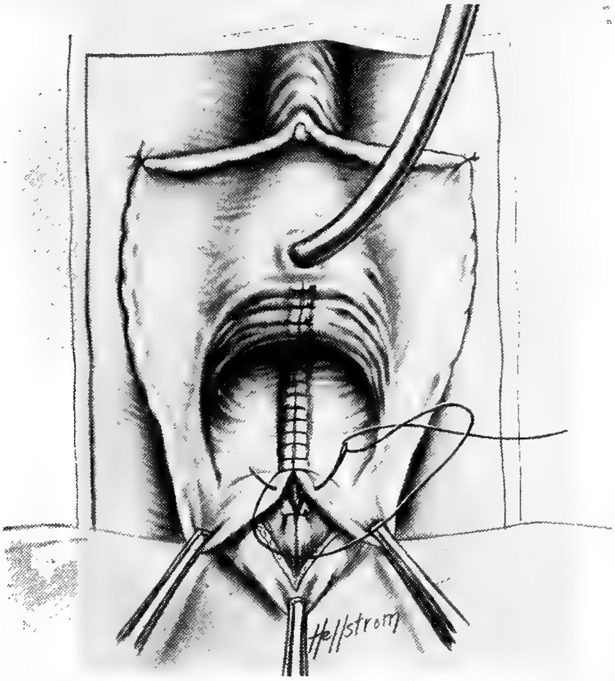
Fig. 179. An opening is left at the apex for extraperitoneal drainage.

Fig. 180. Posterior colporrhaphy. A Foley catheter should be inserted before beginning the posterior repair. A diamond-shaped area containing the scar of the old tear is outlined with clips and scalpel, then reflected and removed, using straight scissors.

Fig. 181. The entire length of the vagina is separated from the rectum. The fascia is incised so that it will fall away with the rectum. (An enterocele attached to the rectal wall should not be overlooked.) Excess musoca is trimmed away as a V upon a V, the amount determined by the degree of enlargement and bulge high in the vagina.







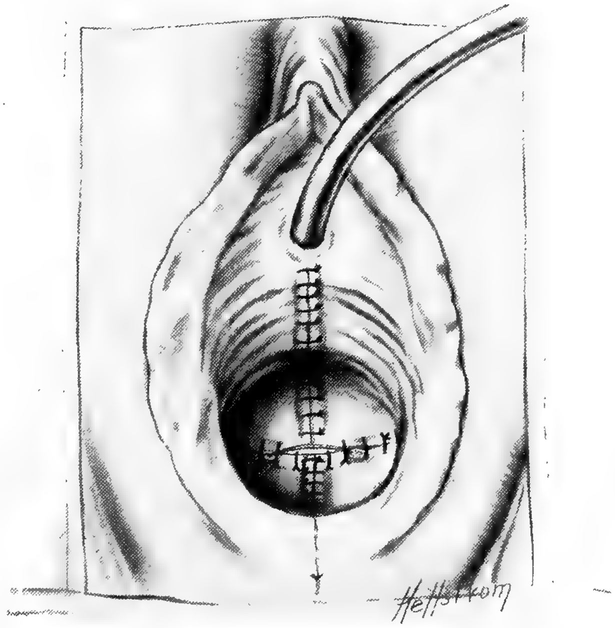


Fig. 182. A lock stitch of double zero chromic is placed in the fascia over the rectum, beginning at the apex of the vagina.

Fig. 183. A series of interrupted zero chromic sutures approximate the levator muscles. The highest suture must be close to the rectum, in order not to produce a high stricture. In some instances many sutures are needed to build up the perineal body, particularly nearer the outlet.

Fig. 184. The more redundant posterior vaginal wall may be closed with a continuous lock stitch of zero chromic catgut. At intervals the lock stitch may include the plicated levator muscle.

Fig. 185. The perineal skin is closed with a double layer of triple zero chromic catgut, one layer subcutaneous and one subcuticular, beginning near the hymeneal ring. Note the opening for extraperitoneal drainage.

CHAPTER VIII

The Fallopian Tubes

The fallopian tubes have four rather distinct portions. The first, known as the interstitial portion, is about one centimeter long and is entirely within the muscular wall of the uterus. It connects the endometrial cavity with the more mobile tube itself. The opening is very small, one millimeter in diameter, has minute folds within it, and some tortuosity; only with difficulty or not at all does it admit a probe to be passed from the abdominal side of the tube into the uterine cavity, although fluid and air may be pushed through this lumen from either side with moderate pressure. In the monkey, there is a valve on the inner side so that it is most difficult to transmit fluid or air through the monkey's fallopian tubes. Such a distinct valve on the inner side is not present in the human. The difficulty in inserting the probe from the abdominal side is of practical importance in plastic surgery on the fallopian tube when attempts are made to open it to restore fertility; present methods favor the introduction of a polyethylene catheter through the tube and out the uterus and cervix, to prevent strictures and closure of the new opening made in plastic operations. Because of this difficulty it may be necessary to re-insert a larger portion of the fallopian tube into the uterine cavity, in order to use this catheter.

The second portion of the fallopian tube, the isthmic portion, extends from the uterus out half the length of the tube, is rather equal in diameter throughout and has many well-defined folds. The third portion, known as the ampulla, comprises the distal half, is more dilated, measures up to one centimeter in diameter and has larger elongated longitudinal folds running out to the fimbriae. The fourth portion, the fimbria, has multiple, elongated, delicate tendrils, mobile by their muscular activity, and covered extensively by tubal epithelium.

The outer coat of the fallopian tube is covered with peritoneum. Immediately beneath this peritoneum are occasional minute collections of squamous-like cells, the cell rests of Walthard, which also may be present in the ovary and which may be precursors of a particular ovarian tumor, known as the Brenner tumor. It is surprising that this Brenner tumor does not occur in the fallopian tube, where the cell rests are more common than in the ovary. The outer muscular coat is longitudinal, extending well into the fimbria, and there is an inner circular coat of muscle. The mucous lining of the fallopian tube is thrown up into longitudinal folds, quite narrow and delicate with loose connective tissue stroma. These folds of the entire fallopian tube and the fimbriae are covered with three types of cells. First, there is the *ciliated* cell, which must make up about one-half of the cells lining the tube. These cells are rather broad and have rather clear cytoplasm and fairly large round nuclei. The ciliae are difficult to see in the ordinary microscopic slide, and are demonstrated more easily by examining minute portions of the fresh specimen under a cover slip in saline, when the motion of the cilia may be most evident. These cells are prominent in their size and activity from the tenth to the twentieth day of the cycle, apparently being useful from the time of ovulation to fertilization and implantation. The second type of cell lining the fallopian tube is known as the *secretory cell,* as tall as the ciliated cell, or slightly taller, much more narrow, with quite elongated nuclei. These cells are larger and longer in the latter half of the menstrual cycle, and they contain glycogen, which is discharged into the lumen in the premenstrual period. Their purpose must be to nourish the fertilized ovum, which lives in the tube for eight or ten days after ovulation. The third type of epithelial cell is the *peg cell,* narrow, very dark, small, wedged between the larger more prominent cells. It is thought this may be a precursor of the secretory cell.

During menstruation the height of the cells diminishes. Being inactive during pregnancy, they are very short and flattened during this period. With endometrial hyperplasia, apparently caused by hyperestrinism, the tubal epithelium is thicker than normal, especially the ciliated cells, which are very tall and quite prominent. In the postmenopausal patient, who has had no estrogen therapy, ordinarily the cells are small and flattened.

SALPINGITIS

Four particular types of inflammation of the fallopian tubes may be classified according to their etiology, namely, from gonorrhea, appendicitis, abortal and puerperal infections, and tuberculosis.

Gonorrheal salpingitis in the past has occurred very frequently, and remains rather common in the charity clinics of general hospitals, though diminishing in incidence. Among the better educated and more cultivated patients it is rare, though it is of importance and is to be considered in the differential diagnosis of every female patient with abdominal pain. The decrease in incidence is attributed to the antibiotic drugs and to education. There is no reason it could not be eradicated completely, if the carriers could be treated simultaneously to prevent reinfection. Gonorrheal infection in the female may occur in the infant and pre-pubertal child as vulvovaginitis, producing thick, creamy, yellow discharge, and complaints of pain and soreness in the vagina, and burning and frequency of urination; it is evidently contracted by much different means than in the adult, possibly from clothing, toilet seats, or unknown agency.

The mucosa of the fallopian tube is extremely susceptible to the gonococcus. This pleasant environment allows the gonococcus to penetrate the folds of the fallopian tube to deposit its gonotoxin, which causes intense inflammation with accumulation of numerous polymorphonuclear neutrophils beneath the epithelium and the extrusion of many such cells into the lumen as a purulent discharge. This discharge drips out the end of the fallopian tube into the peritoneal cavity, where it is most irritating and causes severe discomfort. The inflammation also extends through the muscular coat to the serous coat, which also becomes inflamed, although to less degree than the interior. The extrusion of some pus cells from the surface of the tube does occur. Certainly the entire surface of the tube becomes sticky from the acute inflammation.

In the adult woman, or after menstruation has begun, apparently gonorrhea can be contracted only by sexual intercourse. It may begin in the female in the external appendages, in particular in Bartholin's glands and Skene's ducts, producing discharge and abscess in the former, and purulent discharge from the latter. It is of interest that the ducts of each are lined by transitional epithelium which similarly forms the lining of the urinary tract. These little organs are both quite susceptible to the gonococcus, which thrives in their hospitable domain. The Bartholin's gland abscess may resolve, open spontaneously, or may need incision and drainage. In the chronic state the Bartholin's glands remain thickened or form cysts. It is to be reiterated that the majority of Bartholin gland infections

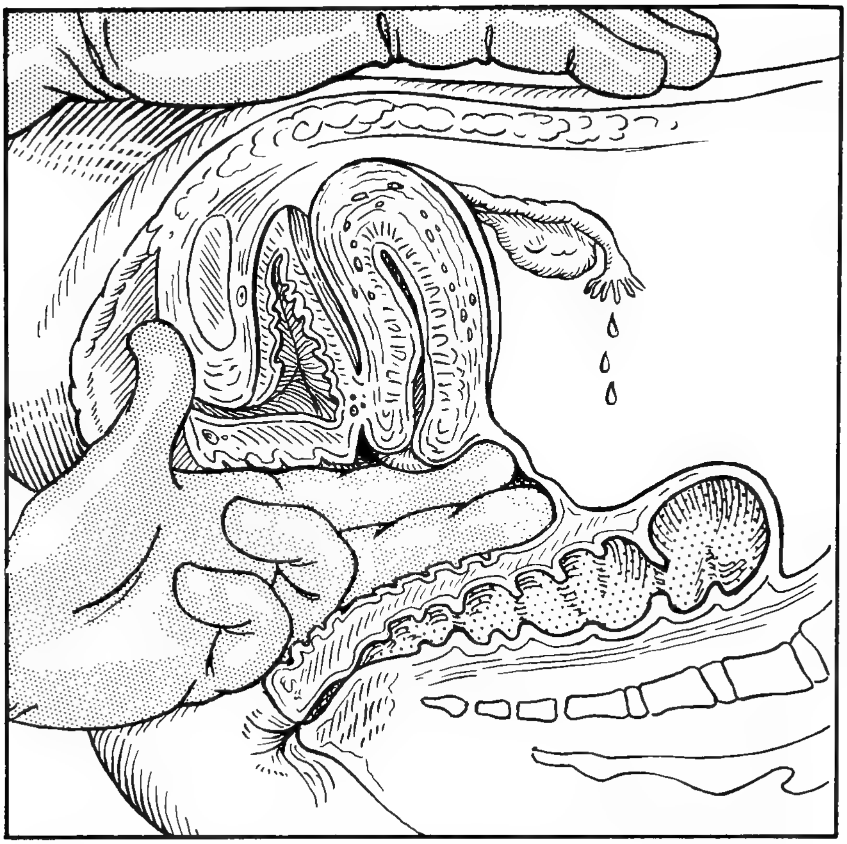


Fig. 186. Diagram of findings in acute salpingitis. The tube is not enlarged. No mass can be palpated. There is only marked tenderness, which of itself may or may not mean organic disease. Note the rigidity of the abdominal wall.

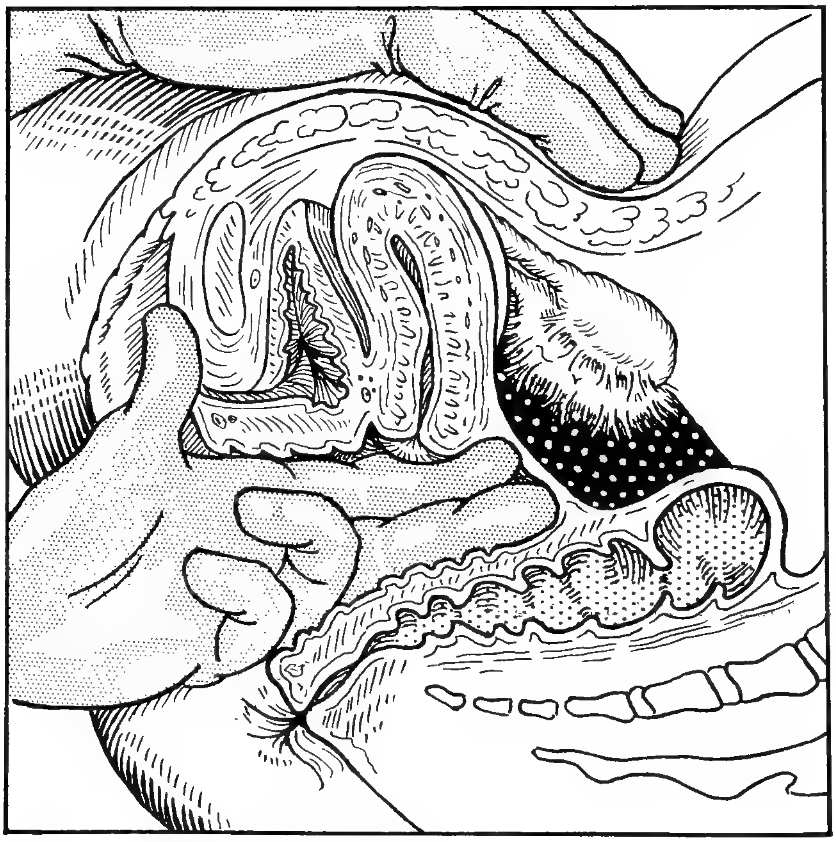


Fig. 187. Subacute salpingitis (diagram)
Induration, the characteristic finding, is present beneath the tube and ovary which have become enlarged, fused together and adherent to the lateral pelvic wall. The rigidity in the abdominal wall has diminished greatly.

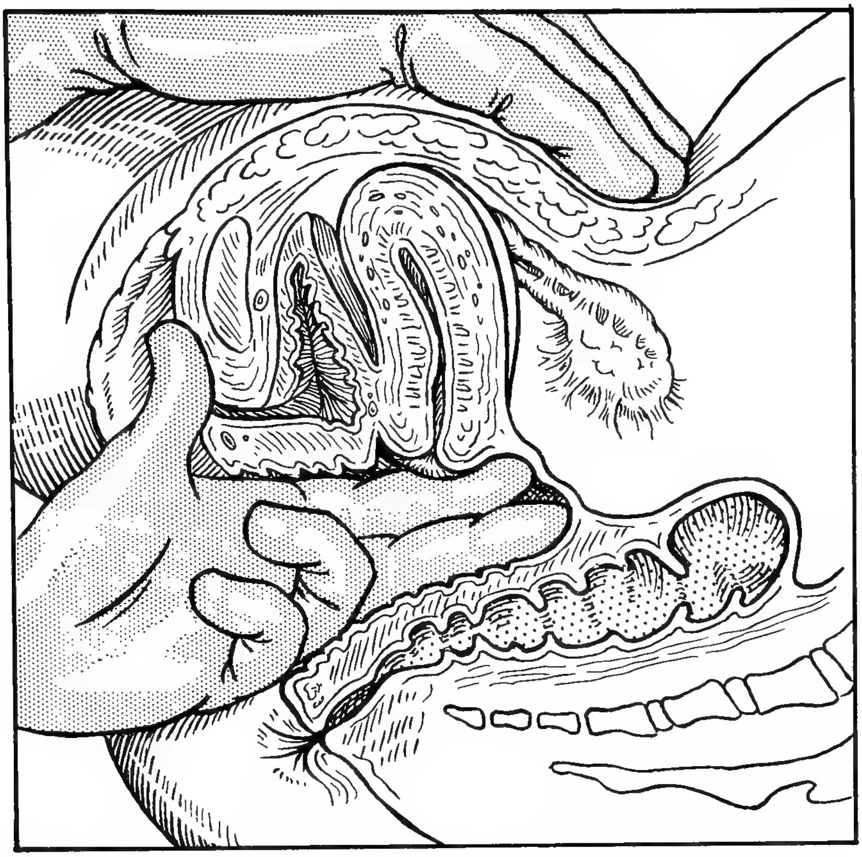


Fig. 188. Chronic salpingitis (diagram)
The induration has disappeared, the rigidity is absent, the tube may not be large enough to be palpable, but characteristically the ovary is adherent from the adhesions which formed when the purulent fluid "boiled-over" from the tube in its acutely inflamed state.

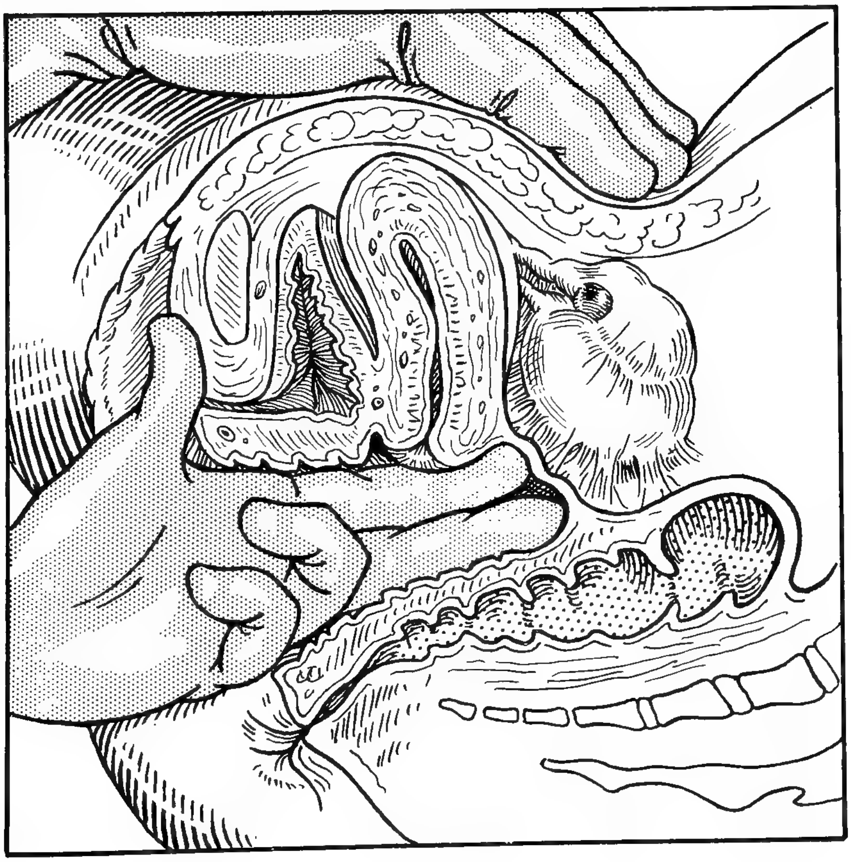


Fig. 189. Chronic salpingitis, with tubo-ovarian inflammatory cyst. (Diagram)
No induration, no rigidity. An adherent cystic mass indicates a tubo-ovarian inflammatory cyst, an endometrial cyst, or a malignant cyst.

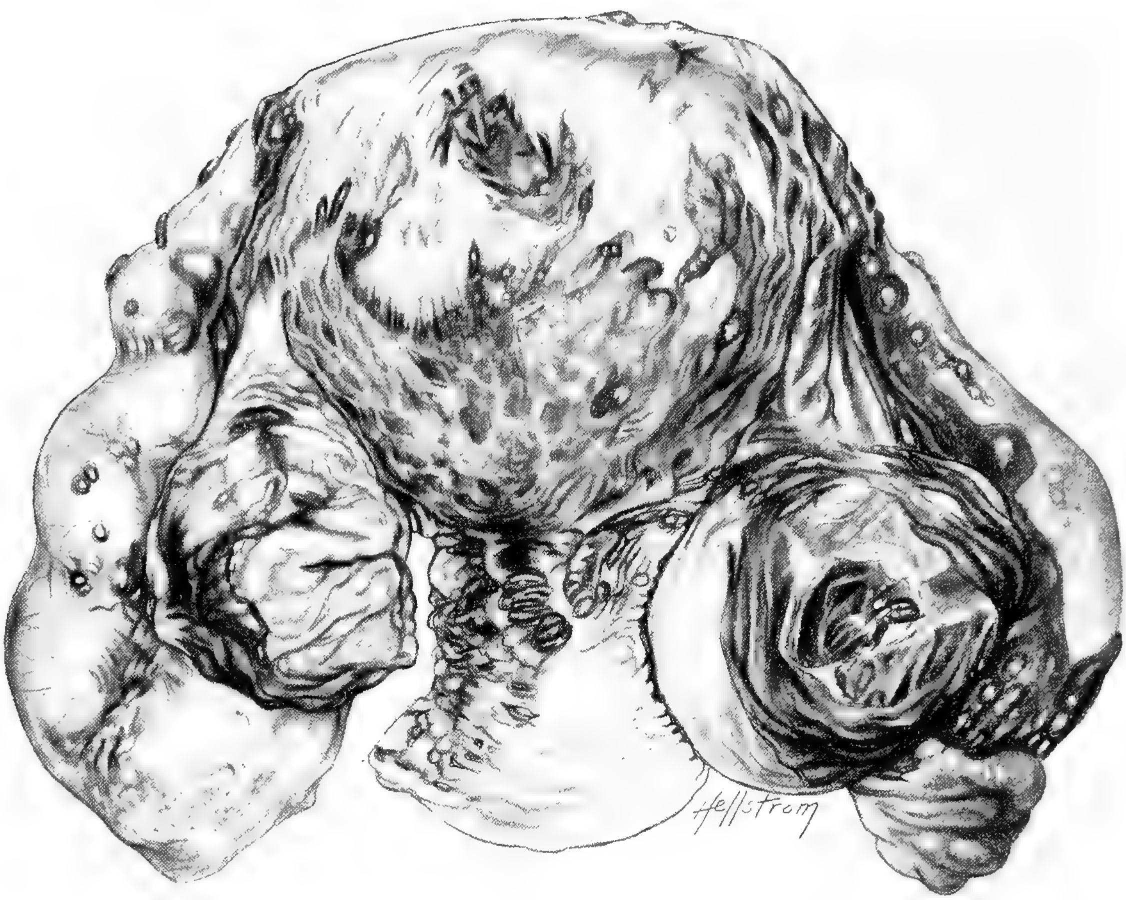
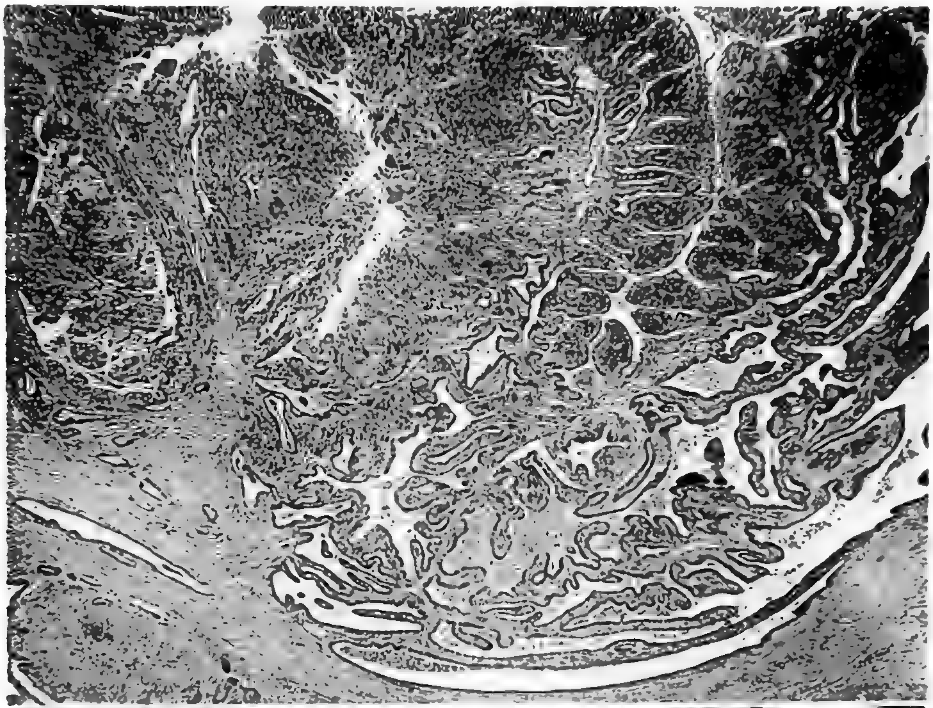


Fig. 190. Subacute salpingitis. Bilateral pyosalpinx. Marked fresh thick adhesions over the ovaries and back of the uterus. The right ovary formed an abscess, secondary from the subacute salpingitis. Duration about six weeks.

seen in more estimable people are not of gonorrheal origin. Similarly, the inflammation in Skene's ducts, producing a red, angry meatus in the acute form or a drop of pus which may be expressed in the more chronic stage, is caused more often not by gonorrhea, but by other organisms, given impetus by the trichomonas vaginalis. The gonococcus may be carried across the vagina to the cervix, where an acute purulent infection quickly develops, producing a copious thin white or yellow discharge of suggestive character. The organism then traverses the endometrium with little evidence of inflammation; if there is acute endometritis, the endometrium is cast away at the next menstrual period, and the newly-formed endometrium shows little or none of the inflammation which might have been present temporarily.

The symptoms of acute salpingitis include marked lower abdominal pain of a rather steady character. As a rule, nausea, vomiting, cramping, indigestion, diarrhea and constipation are absent or not prominent. Acute salpingitis tends to begin immediately after a menstrual period. Often there is a history of yellowish discharge and burning on urination in the previous week or two. The findings are that of a moderate or marked acute illness,

Fig. 191. Salpingitis, subacute, severe, low power. The villi of the fallopian tube are markedly enlarged, being distended with polymorphonuclear leucocytes, some plasma cells and round cells. The exudate into the lumen of the tubes is made up of serum and numerous polymorphonuclear leucocytes. The wall of the fallopian tube is enlarged, edematous and infiltrated with inflammatory cells.



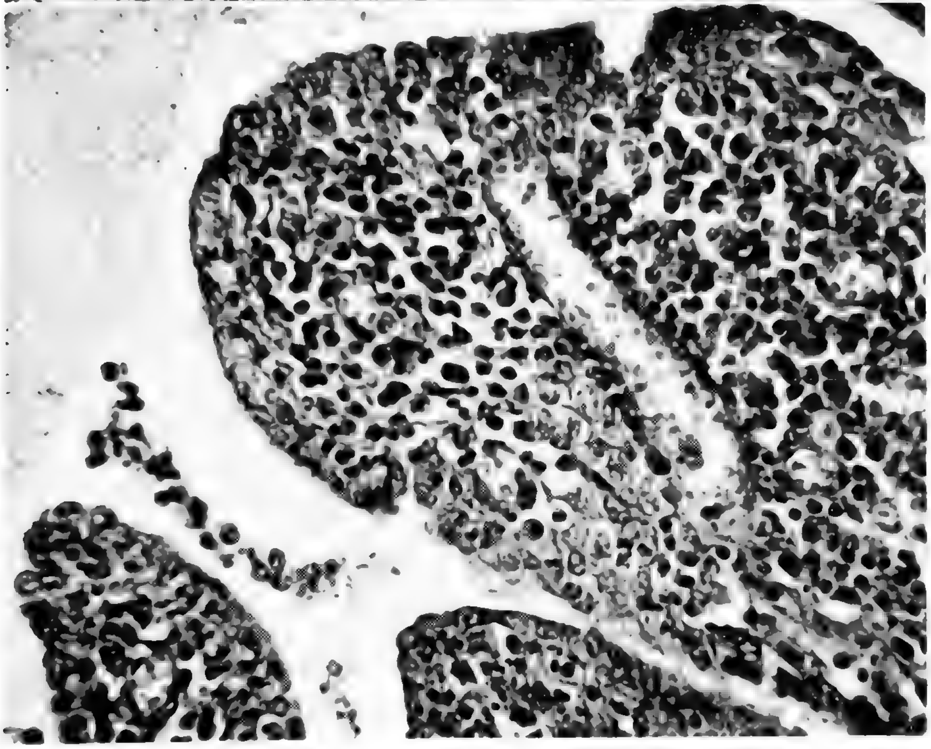


Fig. 192. Subacute salpingitis. The folds of the fallopian tube are markedly enlarged, club-shaped, filled with lymphocytes, plasma cells and polymorphonuclears. The surface epithelium remains intact. Serum and some polymorphonuclears are extruded into the lumen. This is of several weeks duration.

often with fever of 101° or 102°, with a warm, dry skin. The lower half of the abdomen is markedly and acutely tender, often with bilateral rigidity and rebound sensitivity, indicating in varying degree pelvic peritonitis, caused by the overflow of pus with its toxic material, both out the fimbriated end and through its surface of the tube onto the pelvic peritoneum. The tenderness and rigidity as a rule are below the level of McBurney's point, extending across the lower abdomen. Pelvic examination may show some thickening and tenderness of Bartholin's glands, may show a drop of yellowish pus which is milked from Skene's ducts, and may show a copious yellow discharge coming from the cervical canal. At other times, the canal appears clean, and there is no obvious discharge. Palpation shows the cervix firm, closed; the uterus may be indefinitely outlined, apparently mobile. To the sides of the uterus, there is extreme tenderness, but no masses or induration are distinguished. Often the ovaries cannot be palpated because of tenderness so acute that the patient is unable to relax. Movement of the cervix from side to side, or back and forth, produces intense and increased pain, which results from stretching the inflamed fallopian tubes. Such tenderness is of importance in making the diagnosis, but is never diagnostic.

Differential diagnosis of *acute* salpingitis includes the problem of acute appendicitis with pelvic peritonitis. As a rule, acute appendicitis has pain localized near McBurney's point, which the patient can point out by the finger tip within the circumference of the size of a half-dollar. The history of acute appendicitis usually indicates there was epigastric discomfort, occurring some hours before the localizing pain in the right side. The patient has had nausea, frequently vomiting, and the pain is of cramp-like character, as with most acute inflammatory disorders involving the intestinal tract. Confusing is inflammation of the appendix displaced into the depth of the pelvis, behind the uterus and under the right tube and ovary. Acute inflammation of the appendix in this position may produce such low pelvic pain throughout the true pelvic cavity, with marked discomfort on moving the cervix or uterus, that one may be led to believe that such a patient has acute salpingitis. This differential diagnosis may be most difficult.

The diagnosis of gonococcal salpingitis is aided further by the cervical smear, stained with Gram's stain, and the finding of biscuit-shaped gram negative intracellular diplococci having the morphology of the gonococcus. Their presence is strongly suggestive that the intra-abdominal pathology is related to gonorrhea. It is always conceivable that there may be a gonococcal cervicitis, perhaps in the chronic stage, with intra-abdominal inflammation of entirely different nature, though such would be an unusual coincidence. Often the cervical smear is negative and the diagnosis of acute salpingitis must be made by presumptive evidence only. When there is serious doubt as to the nature of pelvic inflammation, an exploratory operation is always to be considered. It is far better to explore a case with acute salpingitis, and remove a normal appendix than to overlook a ruptured or gangrenous appendix.

The treatment of *acute* gonococcal salpingitis has been revolutionized by the use of antibiotics. The first, penicillin, has proved extra-ordinarily effective in the eradication of this organism, but so have practically all of the other antibiotics proven effective in destroying the gonococcus. The inflammation when once formed is not so rapidly dispersed and requires a period of weeks for the absorption of acute inflammation, even when treated in the early acute stage, sometimes not without damage and closure of the fallopian tubes, and the formation of adhesions between surrounding structures. Ordinarily, one intramuscular injection of penicillin of 300,000 to 600,000 units suffices to eradicate the gonococcus in ninety-five to ninety-eight per cent of cases. For good measure, the penicillin may be given daily for a few days. Occasionally, penicillin-resistant strains are encountered, and probably more will develop as the years pass; hence, less frequently-used or new antibiotics may be necessary for treatment of this disease. For the present, terramycin and tetracyline also are very satisfactory.

The diagnosis of *subacute salpingitis* is made when the inflammation is of longer standing, usually of one, two, three weeks, or longer, sometimes many months, during which the inflammation in the wall of the fallopian tube has progressed from infiltration with polymorphonuclear neutrophils to include lymphocytes, plasma cells and eosinophiles. Some scar tissue is being formed, with thickening of the walls of the tube. Pus accumulates in the lumen, the end may become sealed, forming the pyosalpinx, or the tube may become completely adherent to the ovary. Often pus distends the tube and its adherent ovary, forming a tubo-ovarian abscess. And sufficient time has passed for inflammation to infiltrate the ligaments that support the fallopian tubes and the uterus. Brawny induration in the broad and uterosacral ligaments is the tell-tale evidence of subacute inflammation.

Subacute salpingitis produces a history of continuing pain for longer than a few days, perhaps without fever, seemingly more chronic and yet rather acutely tender and debilitating, with marked lower abdominal

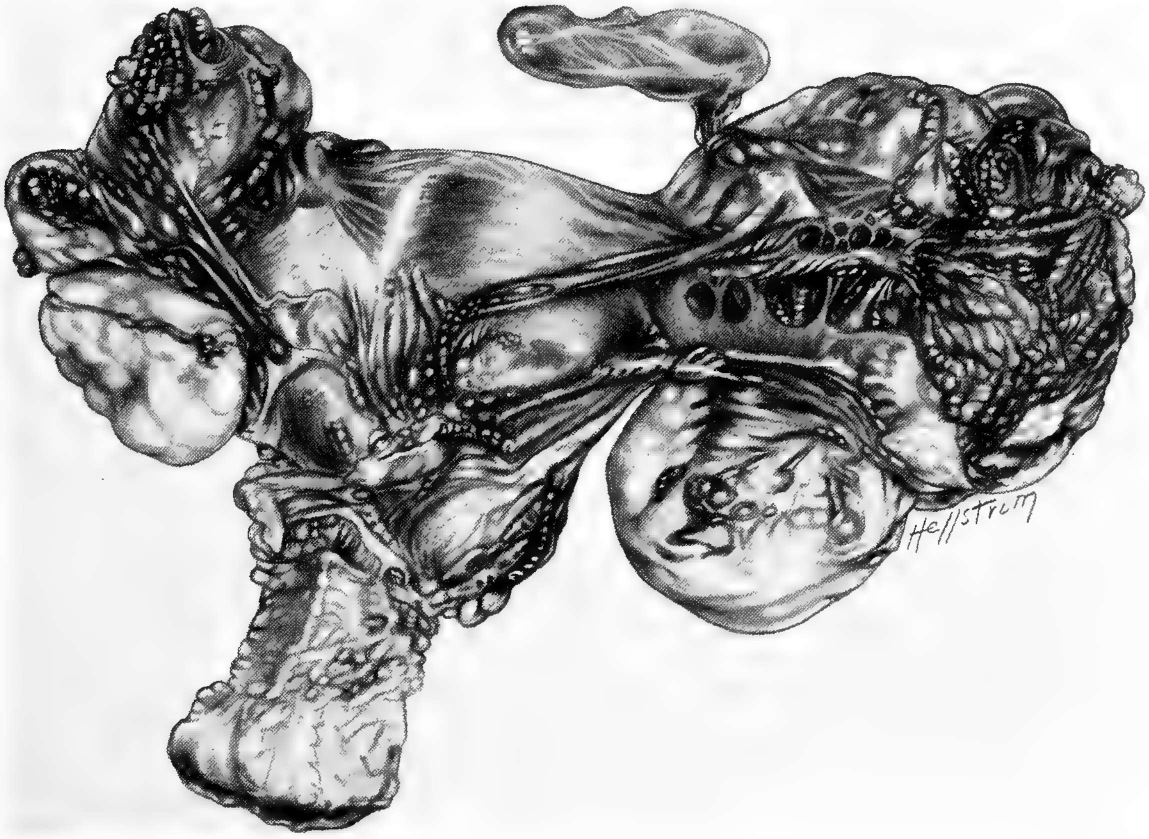


Fig. 193. Subacute salpingitis, severe, with tubo-ovarian abscess right. Bilateral pyosalpinx with marked adhesions. Attached encapsulated sac of peritoneal fluid above the right tube. The left ovary might have been saved in the young woman.

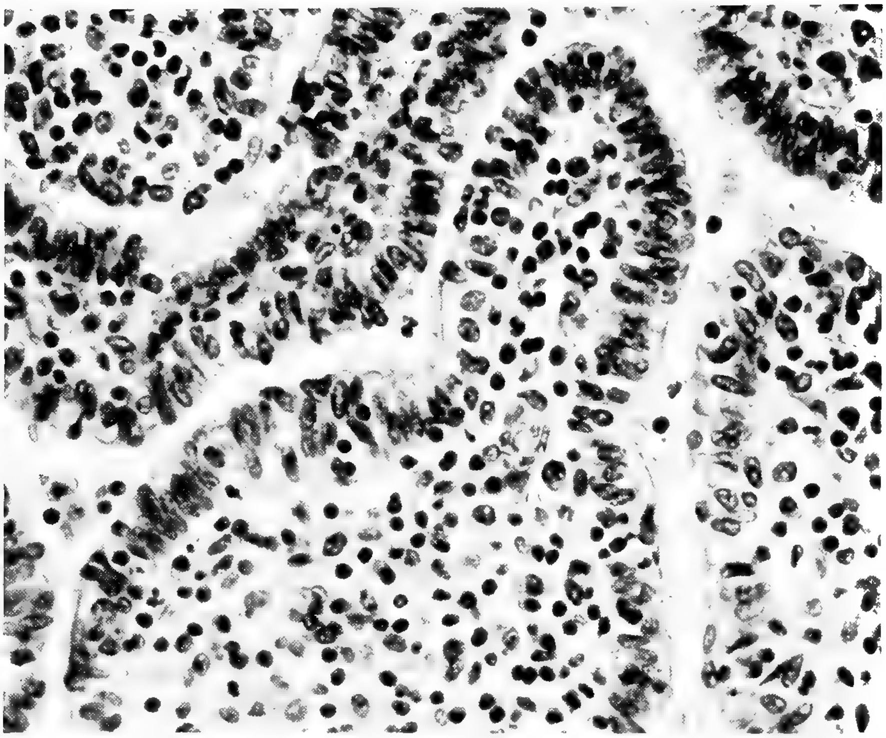


Fig. 194. Subacute salpingitis, severe. The enlarged, club-shaped folds are infiltrated with plasma cells, lymphocytes and polymorphonuclears. The types of the tubal epithelium are rather clearly shown. The flatter or broader cells with more pale cytoplasm have cilia, which may be distinguished. The more elongated cells with elongated nuclei represent the secretory cells. Between these two cells near the base are small dark cells which represent either peg cells or migrating lymphocytes which are passing into the lumen.

tenderness, commonly without rigidity, possibly thickening and tenderness in Bartholin's glands, possibly a drop of pus to be expressed from Skene's ducts, and the more chronic yellowish-white discharge from the cervix. To the sides of the uterus is felt induration, from slight to moderate degree, yet definite. Above the induration there may be palpated the enlarged fallopian tube, of cigar-shaped form, as with the pyosalpinx, or the rounded, fixed mass characteristic of the tubo-ovarian abscess, with induration beneath or lateral to it. Often the enlarged fallopian tubes and ovaries cannot be palpated above this induration. Cellulitis is indicated by the finding of marked brawny induration extending from side to side across the pelvis.

The early tubo-ovarian abscess is of the unresolved type, being firm and non-fluctuant, fixed by dense adhesions, markedly tender, with or without fever and leucocytosis. By this time, the sedimentation rate has become accelerated. With further passage of time the abscess may become larger, the size of a baseball, large orange, grapefruit, and in rare cases the size of a six or eight month's pregnancy. As the abscess becomes fluctuant it tends to gravitate into the center of the pelvic cavity and becomes prominent in the cul-de-sac, readily palpable immediately behind the cervix. As long as the tubo-ovarian mass remains quite firm, it is an unresolved tubo-ovarian abscess; as it gravitates into the pelvis and becomes fluctuant, it is a pelvic abscess. While the tube and adherent ovary make up, for the most part, the walls of the abscess, the adjacent peritoneum over the walls of the pelvis, the intestinal surfaces, the broad ligament, and the back of the uterus, may form parts of the wall of a tubo-ovarian or pelvic abscess. The unresolved abscess either becomes absorbed, or progresses to fluctuation and absorption, or to fluctuation and spontaneous drainage through the rectum or vagina, or to fluctuation and incision and drainage through the posterior vaginal fornix.

Posterior colpotomy is performed when a fluctuant mass is present in the cul-de-sac, associated with a history and findings of subacute pelvic inflammatory disease. Without the induration of inflammation, one would suspect an ovarian cyst, which should not be opened for drainage. As a rule, induration would be present to the side of the abscess. The posterior vaginal retractor is inserted, the cervix lifted with a tenaculum attached to the posterior margin, and a transverse incision is made with scissors two or three centimeters behind the body of the cervix, always in the midline. When the vaginal wall has been cut through, the peritoneum is incised, and the abscess is penetrated with a Kelly clamp, which is spread to enlarge the opening. Culture is taken, which commonly proves to contain E. coli, occasionally streptococci. These are secondary invaders, possibly coming in from the intestinal tract. The gonococcus quickly dies out when pus has formed. Two long cigarette drains with gauze in the center are inserted well into the cavity, being gradually removed over a period of five to seven days. Some prefer a T-tube. Differential diagnosis includes a pregnant retroverted uterus, which may be quite soft and seem fluctuant; a prolapsed ovarian cyst; a hematoma in the cul-de-sac; a dilated loop of intestine with obstruction. An abscess may be absorbed, aided by antibiotics, but a well-formed one should be drained, and further antibiotics will hasten the cure.

Hot douches taken with the patient lying on her back from a douche bag, elevated two feet above her hips, filled with quite warm, clean, but unsterile water, containing a soothing and refreshing douche powder (e.g., alum, oz. 1, liquefied phenol dr. ii, oil of peppermint dr. i, and boric acid oz. iv, one teaspoonful to the quart), are undoubtedly

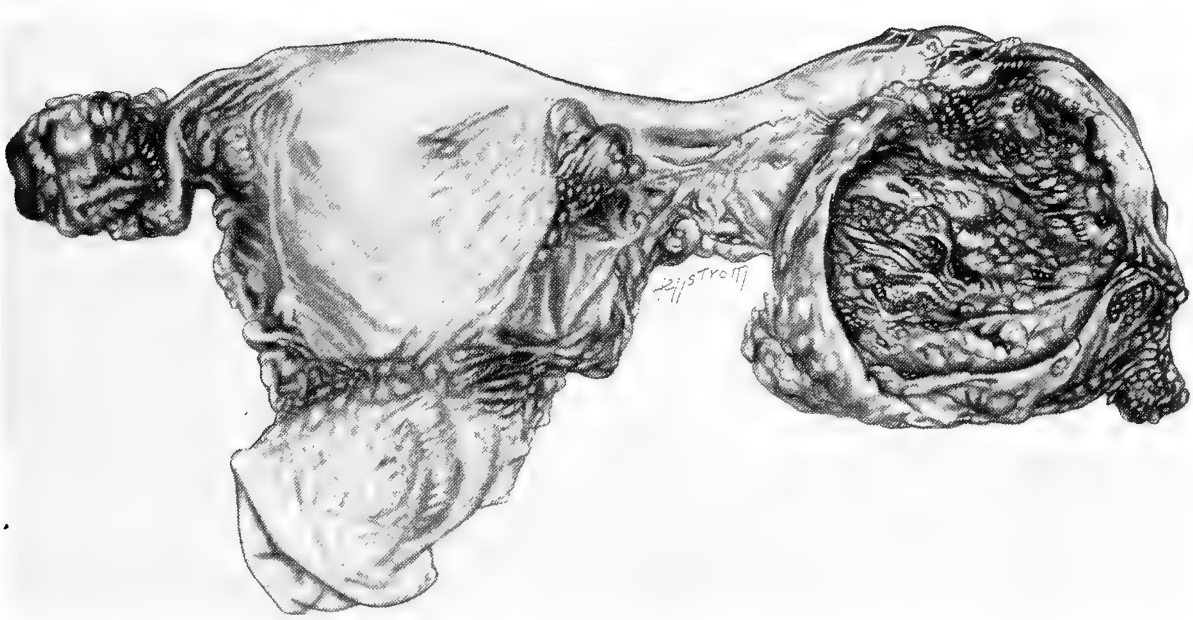


Fig. 195. Salpingitis, subacute, with tubo-ovarian abscess, right. The purulent fluid was spilled in dissecting the abscess.

beneficial in the absorption of the induration of salpingitis. The douche powder is refreshing and of psychological value, while the heat of the doches does not soften the induration itself, but does help by increasing the blood flow to the pelvic organs.

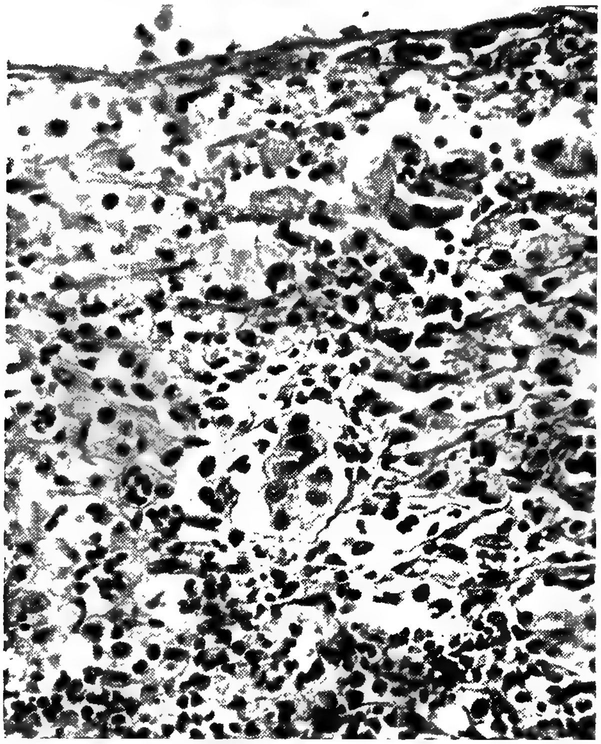


Fig. 196. Wall of a tubo-ovarian abscess. Within this wall, near the interior, are glandular epithelial cells, somewhat in strands which must be disrupted from the tubal epithelium. A marked inflammation extends from about this area throughout the wall of the tubo-ovarian abscess. It is composed of many polymorphonuclear leucocytes along with lymphocytes and plasma cells.

Chronic salpingitis ordinarily indicates the burned-out residuum of acute and subacute inflammation. Now the fallopian tube may have receded to normal size, the distal end have closed, the wall showing some thickening from scar tissue. The tubal folds are thickened, adherent, retracted and blunted or form a chicken-wire appearance of the adherent delicate and thin folds. Relatively few lymphocytes and plasma cells are scattered in the folds and in the walls.

The boiling over of acute inflammation, with the dripping of pus from the distal end of the tube, produces a stickiness to the

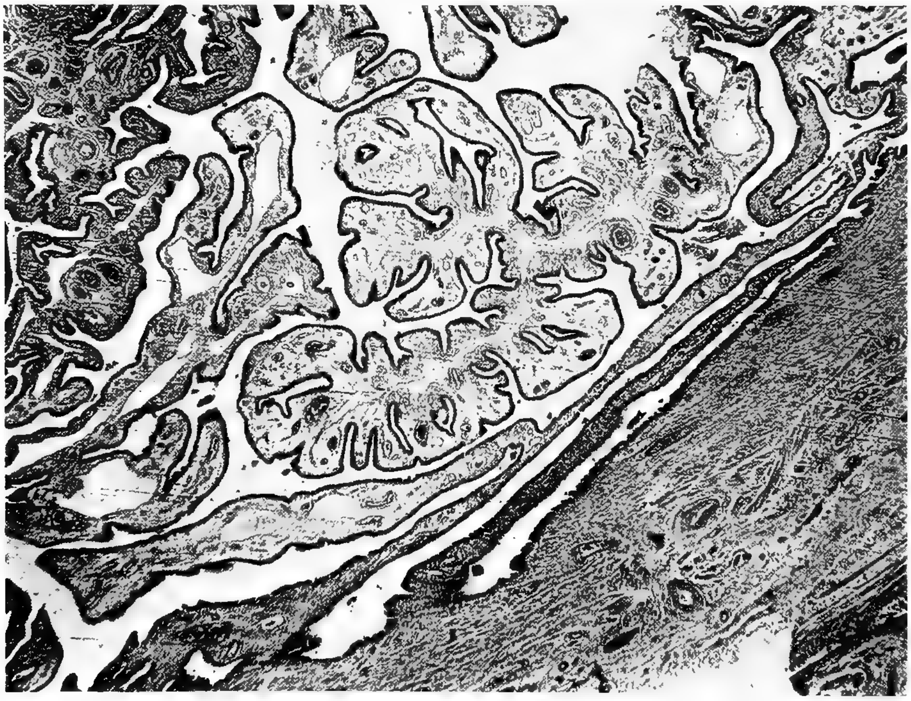


Fig. 197. Chronic salpingitis. The enlarged, club-shaped folds of the fallopian tube are largely replaced with fibrous tissue, there being a relatively scant inflammatory reaction.

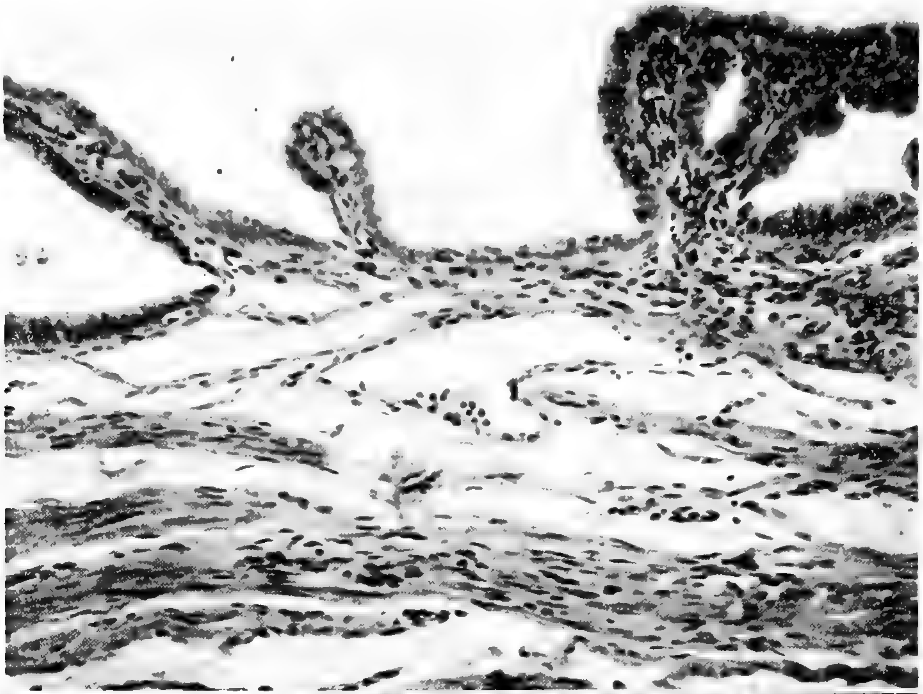
surface of the ovary, causing it to become adherent. The adherent ovary may be the only evidence from physical examination that salpingitis has been present, the only clinical finding as the thickened fallopian tube often is not palpable. A patient so affected may have chronic low abdominal pain, not incapacitating but annoying, increased during menstruation (as are almost all symptoms of gynecologic disease). Menorrhagia is associated frequently. Usually the pain of chronic salpingitis is improved by hot douches, proper rest, abstinence from sexual intercourse and relaxation. Occasionally the pain is so marked and unresponsive to conservative treatment that surgical excision of the fallopian tubes is necessary. If both tubes are removed, and only occasionally are both not involved, the uterus is also removed, as a rule, because the functionless sterile uterus is followed rather often by secondary pathological changes, and meno-metrorrhagia and dysmenorrhea. If a tubo-ovarian abscess has formed in the subacute phase, the absorption of purulent material may leave behind a clear fluid in the cavity, with the formation of a tubo-ovarian inflammatory cyst, a form of chronic salpingitis, or chronic pelvic inflammatory disease. Such is diagnosed by the palpation of an adherent cystic mass to the side of the uterus. Adherence of a cyst is caused by pelvic inflammation, endometriosis (chocolate cyst), or a malignancy which has become adherent. At times, confusion may develop in the diagnosis of any of these three types of adherent cysts. The inflammatory cyst may have a history of inflammation and pelvic peritonitis, which aids in the diagnosis. The endometrial cyst usually has palpable tell-tale implants of endometriosis in the cul-de-sac and on the uterosacral ligaments. The possibility of the malignant ovarian cyst must never be overlooked, and many operations are necessary because of this consideration. Surgery is withheld as long as possible in deference to conservative treatment for chronic salpingitis, because post-operative discomforts may be marked, presumably because more adhesions form where the adherent tubes were separated. The old saying among gynecologists "a surgeon will never make his reputation operating for salpingitis" has some degree of truth, but carefully chosen patients are greatly benefited.

The term *pelvic inflammatory disease* has long been used to indicate the above forms of inflammation, which originate in the fallopian tubes and boil over to involve contingueous structures. This term is often useful, but its abbreviation P.I.D. becomes a slang expression, and may well be eschewed.

POST-ABORTAL AND POST-DELIVERY SALPINGITIS

A somewhat different form of acute salpingitis is that following induced abortion, produced by the placement of a catheter or other foreign material through the cervix into the uterus. A similar infection may follow a spontaneous, or incomplete, or therapeutic abortion, the latter performed for proper reason in the best hospital, or a normal or difficult delivery, or may follow retained placenta, unknowingly left inside the uterus after any delivery. These infections ordinarily are caused by the streptococcus and are said to extend particularly through the wall of the uterus into the parametrium and about the fallopian tubes and ovaries. It seems that this probably is a repeated old idea and that this infection more likely occurs similarly to that produced from the gonococcus, but is often more severe, more acute, and extends more rapidly into the ligaments, lymphatics and blood vessels, and not infrequently producing septic pelvic phlebitis and septicemia. Patients so affected may become quite ill and have a septic course with chills and fever, rapid pulse, marked pelvic pain, rigidity, severe tenderness to the sides of the uterus, and leucocytosis. Induration does not occur until the subacute phase has had time to

Fig. 198. Wall of an hydrosalpinx shows that the folds here are flattened, small, adherent together, while the distended lumen is filled with a serous fluid.



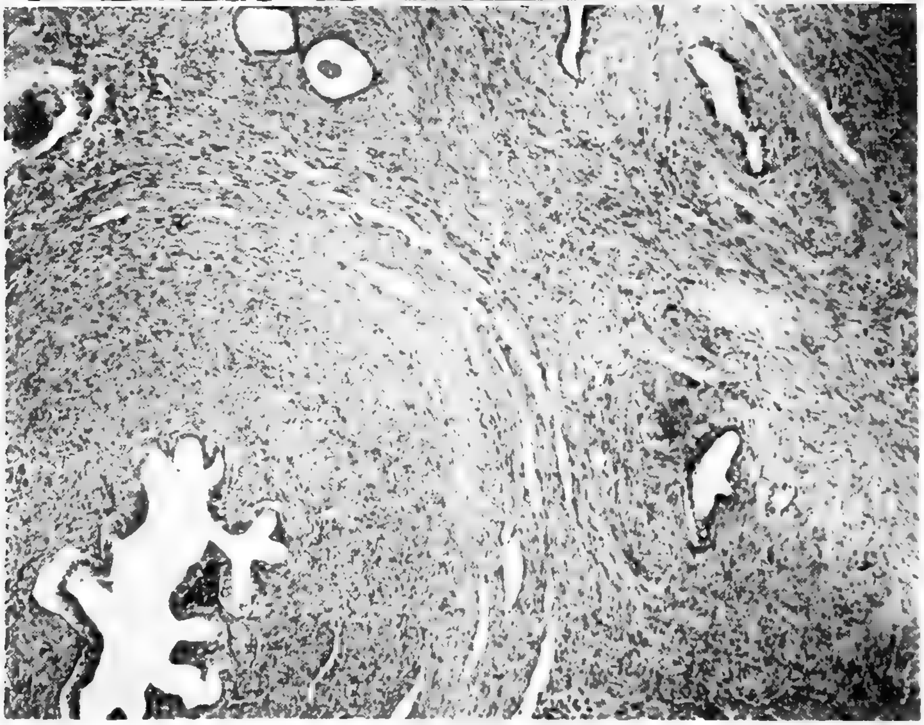


Fig. 199. Salpingitis isthmica nodosa, or adenomyosis of the uterine cornu. The lumen of the cornual portion of the tube is seen in the left lower quadrant of the photograph. Surrounding this thickened cornual portion of the tube is more muscularis and connective tissue with many small areas of endometrial glands. While this has been termed salpingitis isthmica nodosa probably it has no relation to inflammation. The remaining and greater part of the distal fallopian tube, as a rule, is entirely normal. This lesion may completely obstruct the lumen.

develop. This induration may be extreme, suggesting concrete poured into the pelvis, and if it is caused by the streptococcus it may be extremely slow in being resolved and absorbed. Abscesses too may form with this infection, though less commonly. If the streptococcal infection is sufficiently severe, a fatal outcome may occur before an abscess can develop.

Such infections associated with the extrusions of products of pregnancy are treated by antibiotics, such as penicillin, tetracyn, terramycin, chloromycetin, and others. If there is obvious placenta in an open cervix, its removal is indicated. If there is profuse hemorrhage, which does not respond to oxytocics, the uterus must be curetted to stop the bleeding. But ordinarily, with any severe acute post-abortal infection, instrumentation is avoided, as it is believed that such instrumentation may lead to increased septicemia and a greater chance of a fatal outcome.

Fortunately, today severe infections are cured rapidly in most instances by the antibiotics, but occasionally some of the former frequent complications occur. Prolonged chills and fever suggest septic pelvic thrombophlebitis. If showers or repeated small pulmonary emboli appear, ligation of the vena cava may be necessary. This has been shown particularly effective by Collins and coworkers in New Orleans.

The intense induration indicating pelvic cellulitis may remain static for many months, though again less frequently occurring than before antibiotic therapy became available. Many years ago Cullen treated these cases by making a muscle-splitting ("gridiron" or McBurney) incision down to the peritoneum, and placing cigarette drains down to the induration. Many days later drainage of suppurating fluid was followed by cure of the subacute inflammation. This procedure would be necessary rarely today. After the subacute phase, and a long period may elapse before the induration is absorbed, if adherent tubo-ovarian masses persist and are associated with marked symptoms, surgical excision of the tubes, uterus and perhaps even the ovaries may be necessary. Adhesions may be extensive, and dissection may be tedious, difficult and associated with much oozing of blood.

In spite of the antibiotic drugs, fatal results continue occasionally. In others, chronic pelvic inflammatory disease may require eventual surgical intervention. Not infrequently even a mild inflammation may be followed by sterility from tubal occlusion. The one child sterility is thought due to such a mild post-delivery infection in many instances.

POST-APPENDICITIS SALPINGITIS

Another not too uncommon and quite important form of pelvic inflammatory diseases is that which follows acute appendicitis, especially the development of a gangrenous appendix or ruptured appendix with peritonitis. Such catastrophic inflammation often wrecks havoc on the innocent reproductive organs, and even the milder forms of acute appendicitis may spill enough pathogenic bacteria to cause a mild salpingitis and closure of the fallopian tubes. Various bacteria, including the colon bacilli and the streptococci attack the fallopian tube from its surface and from its orifice to cause a quite similar salpingitis, as seen with gonorrheal salpingitis. Most commonly the pelvic inflammatory disease is not recognized because the patient is being treated for appendicitis by operation, or as occasionally indicated, by conservative therapy. One may not think of the distressed fallopian tubes, not that anything could be done about it then, other than possibly continuing antibiotic therapy longer than might seem necessary with simple acute appendicitis that has been seemingly cured by excision. A surprising amount of sterility is caused by closure of the fallopian tubes caused by infection secondary to acute appendicitis. Such a diagnosis may be considered, if the ovaries of normal or slightly enlarged size, are adherent, or if there is present an adherent tubo-ovarian cyst, with a history of appendicitis and pelvic peritonitis. Only too often the fallopian tubes are found completely obstructed in patients who have had appendicial abscesses with drainage, when tested in later years by transuterine tubal insufflation (the Rubin's test) or hysterosalpingography.

Pelvic cellulitis and pelvic abscess occur occasionally after severe appendicitis, with pelvic findings more obvious than the more frequent and more occult type described. The abscess may rupture spontaneously into the rectum or vagina, but should be carefully followed and drained by incision through the posterior fornix of the vagina at the proper time.

With complaints of chronic pelvic pain, acquired dysmenorrhea and menorrhagia, and with definite palpatory findings of pelvic inflammatory disease, surgical intervention may be necessary. Removal of one or both tubes, the uterus, and even all ovarian tissue may be necessary. In patients with a chief complaint of sterility, chronic salpingitis may be diagnosed, confirmed by hysterosalpingography, with the finding of obstructed tubes, with or without hydrosalpinx. Surgical attempts at opening the tubes in various manners are followed most often by failure to maintain patency, especially in those cases associated with acute appendicitis in earlier years. It is far better to remove the appendix when there is reasonable suspicion of appendicitis in the young woman, than to compromise her fertility. Appendicitis may be one of the most treacherous of diseases, protean in its manifestations and subtle in its symptoms.

TUBERCULOUS SALPINGITIS

Tuberculosis of the fallopian tubes caused by the tubercule bacillus is seen relatively rarely today. It occurs more frequently in areas of dense population, or in areas with poorer hygienic surroundings. In recent years larger series have been recorded from Europe and from the Middle East. Wherever pulmonary tuberculosis is seen more frequently, evidently tuberculous salpingitis is more common.

The disease occurs during menstrual life, both in the quite young girl, and up to the time of the menopause. Rarely, if ever, is it found in the pre-pubertal child or in the postmenopausal woman. Sometimes burned out, quiescent lesions are found microscopically incidentally in the excised tubes removed after the menopause. This disease is said to compose about five per cent of all cases with salpingitis. Since salpingitis, in general, was much more frequent in occurrence twenty years ago or more, the finding of tuberculous salpingitis was more frequent at that time. Probably the percentage is about the same today, but any form of salpingitis in the private practice of gynecology is far less frequent today, and this includes tuberculous salpingitis.

Tuberculosis of the fallopian tubes apparently arises most often from a primary focus in the lungs. Here there may be active tuberculous infiltration in the lungs, or x-ray films may indicate a relatively healed lesion. It is thought that a lymph node containing viable bacilli may erode into a vessel and cause showers of the tubercule bacilli to be disseminated in the blood stream. Evidently the fallopian tubes are among the most sensitive areas in which the tubercule bacilli may become lodged and proliferate, just as the kid-

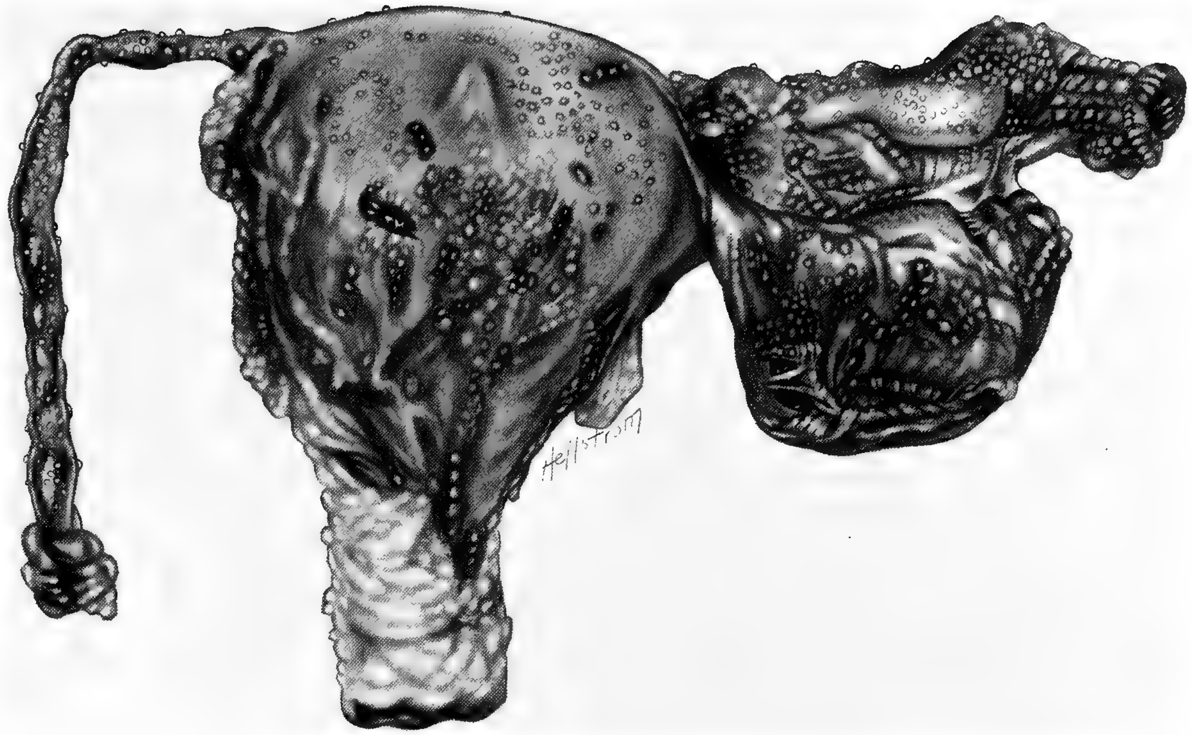


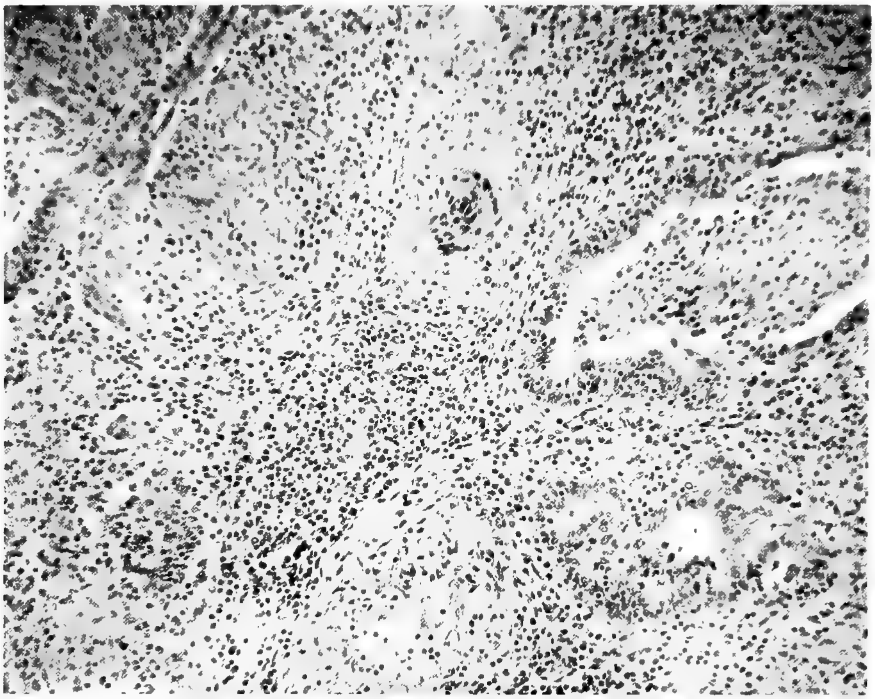
Fig. 200. Tuberculosus salpingitis. Secondary tuberculosis of the surface of the ovary and peritoneal surfaces. The small yellowish granular nodules are characteristic, when present, but any ordinary-appearing chronic salpingitis may prove to be of tuberculous origin, when sectioned and stained for acid-fast bacilli.

ney and epididymis similarly are quite susceptible to the development of an isolated secondary lesion.

Tuberculosis of the tubes may possibly arise secondarily to tuberculosis of the intestinal tract, but this seems quite uncommon today. It may arise secondary to tuberculous peritonitis, which may have its origin from the rupture of the retroperitoneal lymph nodes containing viable tubercule bacilli, but this seems to be a rare occurrence. Finally, the disease may possibly arise by ascending infection, being transmitted by the male who may have a tuberculous infection in the epididymis. But of all the cases with tuberculous salpingitis the male is proven infected extremely rarely.

The disease begins as an inflammation in the endosalpinx, with the formation of small, hard tubercules, composed of lymphocytes and epithelioid cells with multi-nucleated giant cells in the centers. The nuclei tend to be arranged in a horseshoe manner around the periphery of the cell. While tubercules may have other origins, as from foreign body reactions, from the introduction of radio-opaque media for the study of fallopian tube patency, possibly from douches with irrigation extending through the cervix across the endometrial cavity and to a slight extent into the fallopian tubes, these seem relatively rare occurrences. In the foreign body giant cells the multiple nuclei are grouped more in the center of the cells and often a minute fraction of the foreign body material may be seen within the cell itself. Other forms of tubercules that may be difficult to distinguish from tuberculosis histologically are those associated with Boeck's sarcoid or undulant fever, both being more rare in occurrence

Fig. 201. Tuberculosis of the fallopian tube, low power view. A severe chronic inflammation has disrupted the normal appearance of the tubal epithelium and the villi. The tubercules are surrounded by epithelioid cells and contain large, multinucleated giant cells in the center. The demonstration of the acid-fast bacillus is required either by culture or by staining techniques for accurate diagnosis.



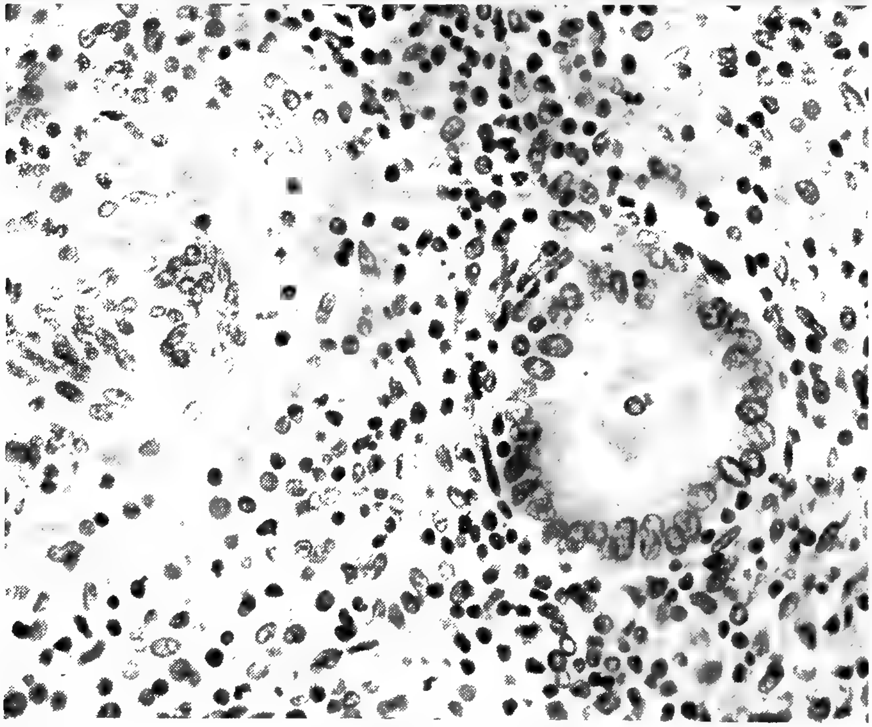


Fig. 202. Tuberculosis of the fallopian tube. High power view of large multinucleated giant cell, surrounded by epithelioid cells and lymphocytes. A small area of tubal epithelium suggesting a gland is present on the right.

than tuberculosis. The true diagnosis is made only by differential staining or culture and the demonstration of the acid-fast organism. The inflammation tends to extend through the wall of the fallopian tube in small areas and tubercules form on the surface of the fallopian tube, having a small, raised yellowish-white appearance which may break open and allow the showering of tubercule bacilli into the peritoneal cavity. The tubal walls become thickened in varying degrees, sometimes only slightly thickened, and others markedly thickened, with or without the development of pyosalpinx or tubo-ovarian abscess. Characteristically it has been said the fimbriated end of the fallopian tube tends to remain open, that the fimbriae tend to become somewhat thickened though remaining patent, and that frequently a slight constriction appears just medial to the fimbriae.

The typical appearance of tuberculous salpingitis, with its multiple tubercules on the surface of the tube, is readily diagnosed at the operating table by its appearance, but in a greater percentage of cases no obvious tubercules are seen and the findings suggest ordinary chronic salpingitis and tubo-ovarian inflammatory disease. The adhesions are frequently most difficult to separate, suggesting possible streptococcal disease, and injuries to the muscular layers of the bowel wall are frequent. Tuberculosis of the peritoneum is often associated with tuberculosis of the fallopian tubes, being secondary to the tubal inflammation. While tuberculous peritonitis may be primary, arising from ruptured lymph nodes in the mesentery, in women much more frequently the origin is from the fallopian tubes. Tubercules may have extended over the entire peritoneal cavity covering the intestines, the parietal peritoneum and omentum, causing the exudation of a clear, yellowish or greyish type of fluid in moderate or marked degree.

Tuberculosis of the endometrium is almost always secondary to tuberculosis of the fallopian tubes, occurring as a descending infection. Endometritits of this type occurs in one-third of the patients with tuberculous salpingitis. It is diagnosed only if the uterus is curetted, which is rarely done in the presence of obviously palpable salpingitis before abdominal operation is contemplated because of the possibility of producing an exacerbation of any subacute or chronic infection in the adnexa. In less extensive cases without obvious palpable pathology, a curettage may be performed for irregular menstruation and allow the diagnosis. Or biopsies of the endometrium in patients being studied for sterility occasionally may show tuberculosis as an incidental finding. A much smaller percentage of patients may have tuberculosis of the cervix, apparently again secondary to tuberculosis of the endometrium; relatively few cases have been reported in the literature. When it occurs the cervix becomes enlarged, irregular, granular, appearing as a hypertrophic chronic eversive cervicitis. Tuberculosis of the vagina and vulva are successively less frequent than that of the cervix, again usually being secondary in the descending order of occurrence and method of spread. Chronic ulcerative lesions of the vagina or vulva must always be considered as having a possible origin in tuberculosis, though exceedingly rare at this time.

Thus the fallopian tube is the site of origin of pelvic and abdominal tuberculosis in the female in the vast majority of cases in which it occurs. The appearance of the fallopian tube may be normal, the discovery of the tuberculosis being incidental or accidental, either from incidental excision of the tube and removal of the uterus or ovary or both if necessary for other purposes, or when tuberculosis of the endometrium is discovered on routine study of endometrium removed for other purposes. If found in the endometrium, always one assumes that there is tuberculosis in the tubes. Secondly, the tube may have the form of a pyosalpinx or tubo-ovarian abscess containing frank pus in the lumen. Third, the tube may be arranged in a form of severe chronic salpingitis with extremely dense adhesions in which it is exceedingly difficult to distinguish the morphology of the fallopian tube of itself. Finally, the tube may appear thickened, nodular, with closed or open fimbriated ends, with or without the typical small, yellowish tubercules on its surface. When the nodules are present on the surface, commonly they have extended to the surface of the uterus, the pelvic peritoneum, or entire peritoneal lining of the abdomen. Then there may appear the wet type of tuberculous peritonitis with the exudate of fluid, producing a form of ascites, or the dry type producing extensive adhesions between the pelvic organs and adjacent peritoneal surfaces, particularly involving the intestines.

The symptoms of tuberculous salpingitis and tuberculous disease in the pelvis associated with salpingitis are not characteristic or diagnostic. Pelvic pain in varying degree is the rule. Metrorrhagia occurs in one-third of the cases, amenorrhea in one-third of the cases, and normal menstruation in the remaining third. Malaise is a frequent complaint. Sterility is often noted. Enlargement of the abdomen may be a complaint or an obvious finding. More frequently there is no suspicion of a febrile disease.

Examination shows that the patient appears quite well or that she has lost some weight, appears fatigued or that she is seriously and subacutely ill. The abdomen may be slightly or moderately distended with a doughy sensation on palpation, with a moderate lower abdominal tenderness, and often with evidence of free fluid in the abdomen as shown by shifting dullness in the flanks and possibly the presence of a fluid wave. While these are characteristic and very suggestive of tuberculosis or possibly malignancy, frequently there is no distention or evidence of free fluid. Pelvic examination may be normal in some instances, but more frequently shows findings of chronic salpingitis with adherent pelvic adnexal masses. Patients who have evidence of salpingitis, in which one would not suspect gonorrheal dis-

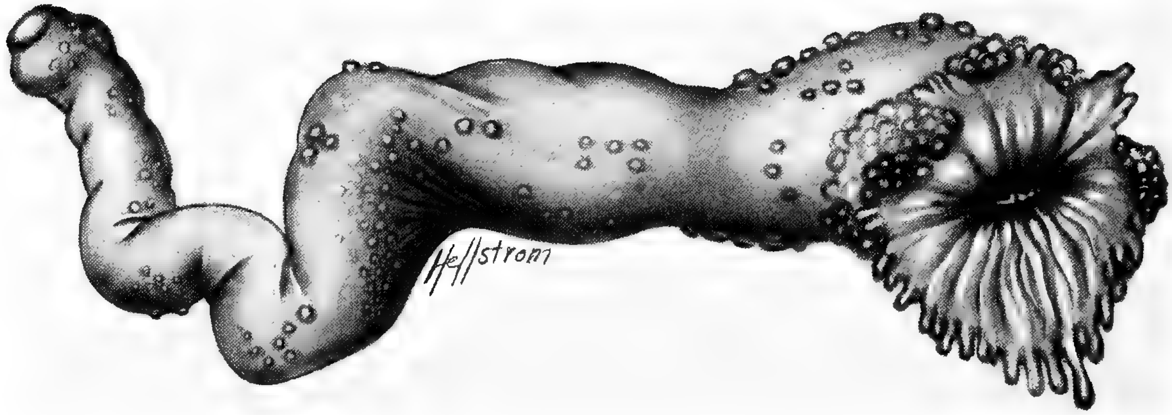


Fig. 203. Tuberculosis of fallopian tube. Many small raised, yellowish tubercules on the serosa and the fimbria. Note the fimbriated end is open, with constriction just proximal to it. More severe changes are present in the tubal folds.

ease may be suspected of having tuberculosis. X-ray films of the lungs may show active tuberculosis in one-half to one-third of the patients, but probably more frequently show only healed and non-suspicious lesions. The tuberculin test, if performed, should be strongly positive. Any positive diagnosis will require the more or less accidental finding of tubercules in the study of endometrium obtained for this purpose or for other therapeutic reason when obvious salpingitis is not noted. Thus the pre-operative diagnosis of this condition may be exceedingly difficult or impossible to make. Certainly it is difficult before any surgery is performed and often even at the time of operation. Hysterosalpingography is performed rarely in cases of tuberculosis, usually when it is not suspected, but it may show peculiar irregularities in the interior that some have felt are suggestive of tuberculosis, though it is questionable that any accurate diagnosis could be made by this means.

The treatment of tuberculous salpingitis and its extensions has been surgical excision over very many years, in a good proportion of instances performed without the preoperative or operative diagnosis of this disease. Of course, in many other instances the diagnosis is either suspected before surgical operation, or is obvious when the abdomen is opened and the tubercules are seen. Relatively good results have followed this local excision of the involved pelvic organs which usually means excision of the fallopian tubes. As stated previously as a principle in the treatment of chronic salpingitis, when excision of the fallopian tubes is necessary, as a rule the uterus is removed. However, in cases with tuberculous salpingitis not infrequently the pelvic adhesions are so extensive as to make excision of the uterus not feasible and even a dangerous additional procedure, even though tuberculosis of the endometrium may be suspected. Excision of the fallopian tubes alone often is followed by regression and healing of the remaining tuberculosis, whether in the endometrium, on the surface of the uterus or ovaries, on the pelvic peritoneum or throughout the lining of the peritoneal cavity. In each instance the extended lesions tend to heal after excision of the fallopian tubes and this is one of the well-established principles of therapy.

On the other hand, sanatorium rest over a prolonged period of time may be followed by some degree of healing of the pelvic tuberculosis. But this method of treatment alone is not a feasible one, nor advisable, because the results are so unpredictable and because the individual can be restored to health much more readily, provided there are not other signs of systemic tuberculosis. Active pulmonary tuberculosis certainly would mitigate against any pelvic surgical procedure.

In very recent years great interest has developed in the use of drug therapy for tuberculosis, particularly as related to that of pelvic tuberculosis and renal tuberculosis. Apparently the combination treatment, using streptomycin in 0.5 to 1 gram daily, paramino-salicylic acid in 2 or 3 gram doses by mouth daily, isoniazid in 2 to 4 gram doses daily, may be used simultaneously over a period of many months (from six months to one year) and may be followed by remarkable healing of tuberculosis in the fallopian tubes, uterus and periotoneal surfaces. Similarly, remarkably excellent results have been reported by a few observers in tuberculosis of the kidney, so that it appears that perhaps this medical treatment is more desirable than surgical excision. On the other hand, we must observe that in the treatment of pulmonary tuberculosis, the surgical excision of involved lobes has become a well-established and widely used procedure in recent years, as an adjunct to drug therapy.

The difficulties in the use of the medical therapy for pelvic tuberculosis are primarily in the diagnosis of the disease. While pelvic tuberculosis may be strongly suspected in those instances with the doughy abdomen and free fluid in the abdomen with evidence of

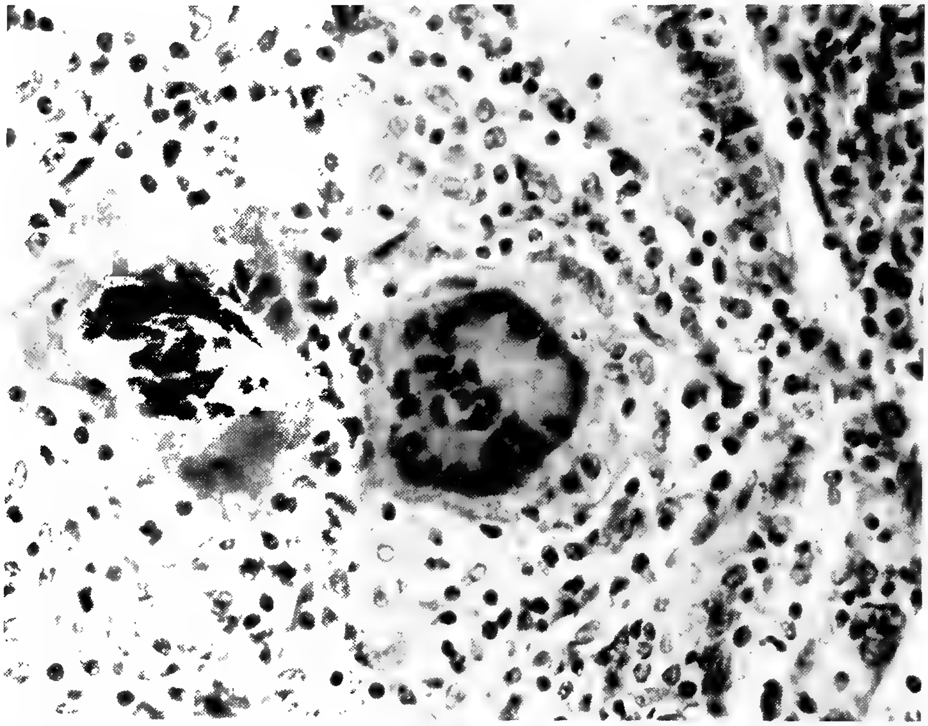


Fig. 204. Tuberculosis of the fallopian tube, high power. On the right is seen the compressed lumen, lined by tubal epithelium. On the left there are large, multinucleated giant cells, surrounded by epitheloid cells, lymphocytes and plasma cells.

pelvic inflammatory disease, yet an accurate diagnosis could be made only if the tubercules and the tubercule bacilli are identified. This means that in suspect cases endometrial biopsy for microscopic sections and cultures are indicated. Perhaps when abdominal exploration is performed, if tuberculous lesions are obvious, some should be excised for biopsy and special staining and culture, after which the abdomen may be closed without further operative procedure. It is known that simply the exposure of the abdominal cavity to the air is followed by improvement in a fair percentage of patients, so that there would be some surgical benefit beyond the biopsy. But in those many instances in which the diagnosis cannot be determined or even suspected by gross examination of the pelvic organs, even under direct vision, then one could not possibly use the medical regime of treatment.

The advantage of the use of medical therapy is always the conservation of pelvic organs for the prime purpose of retaining fertility. That fertility can be restored in patients with nodular salpingitis, pyosalpinx or with the densely adherent form of the disease is not only questionable, but exceedingly unlikely. In those patients with the grossly normal fallopian tube, if the diagnosis can ever be made, and this is almost an accident in obtaining it, undoubtedly medical therapy is the indicated treatment to attempt to retain fertility. On the other hand, the attempt to conserve pelvic organs that can never be of any use in procreation, that are the seat of possible recurrent disease and cause of chronic pelvic complaint is illogical, and the extension of medical therapy beyond reason, except in unusual circumstances where the patient is extra-ordinarily emotionally attached to her diseased pelvic organs.

Another factor of great importance to be considered is the complications and results of surgical therapy. In the operative cases in which there are exceedingly dense and extensive adhesions, the great dissection and trauma to the intestinal walls are followed by intestinal fistula formation through the abdominal incision in occasional patients, which usually leads to a fatal outcome. A second point is that in some patients the operation is followed immediately by miliary tuberculosis, a septic fulminating course with swinging temperature changes and often a fatal outcome. Both of these post-operative complications may be alleviated or deterred by post-operative medical therapy. Certainly they are to be considered.

ECTOPIC PREGNANCY

Ectopic pregnancy includes all pregnancies occurring outside the uterus, whether in the tube, ovary, or attached to the pelvic peritoneum. Ectopic pregnancy occurs in one in two hundred and eighty pregnancies, and represents the most frequent serious emergency in gynecology.

The primary abdominal pregnancy is of extraordinary rarity. In this situation apparently the ovum may be fertilized before its arrival into the fallopian tube or perhaps may have been fertilized in the tube and passed backward into the abdominal cavity. At any rate it becomes implanted on the surface of some organ in the pelvis and grows sometimes to form a full term pregnancy, though more frequently ending in catastrophy before term. Again it is extremely rare, usually ruptures and bleeds from the extension of the placenta at some time during the course of the pregnancy. Usually the fetus dies before it can be removed by surgery. If operation is not mandatory by hemorrhage, the fetus may become calcified, forming a lithopedion, discovered in later years in x-ray films. Under rare circumstances the pregnancy may proceed to term and may be delivered by caesarian section.

The secondary abdominal pregnancy is more frequently occurring than the primary type, and follows the slow rupture of a tubal pregnancy with gradual extension of the placental implantation onto adjacent organs and peritoneum. While these pregnancies have proceeded to term, with the delivery of live children in very rare instances by laparotomy, more frequently there appears signs of intra-

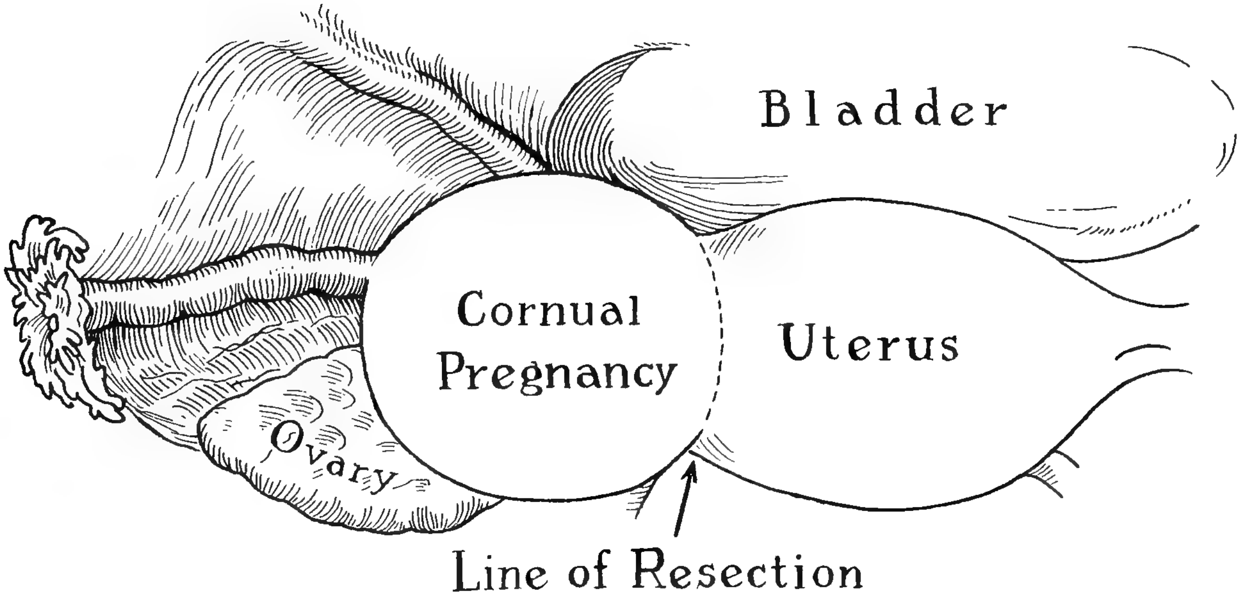


Fig. 205. Cornual pregnancy. When this ruptures, intra-abdominal hemorrhage is rapid and severe. This form of ectopic pregnancy may be palpated before rupture, but diagnosis then is difficult, because the normal pregnant uterus may be quite irregular.

abdominal hermorrhage at some phase of the development, which requires surgical intervention. As a rule the fully attached placenta is not removed, and ligation of the cord with removal of the fetus may be followed by cessation of bleeding. Such removal may be followed by severe hemorrhage, impossible to control by suture and difficult to control by packing. These placentas become intimately blended with mesenteric vessels and retroperitoneal channels. Usually the placenta is absorbed and disappears. On other occasions it becomes separated in the next few weeks, forms a readily palpable mass and is removed by a second operation.

The symptoms of abdominal pregnancy are those of the usual tubal pregnancy, except that the pregnancy may become advanced. Abdominal and pelvic pain associated with missed menstrual period and vaginal bleeding suggests the possibility. Palpation of a mass separate from the uterus may suggest the diagnosis. The fetus is palpable very superficially. In the late cases, x-rays may show the fetus unusually prominent, with separate uterus sometimes visible. Some have used hysterosalpingography to confirm the diagnosis. While this makes a startling film, the procedure is not without danger, because the pregnancy may be intrauterine, and extravasation of the medium may extend into the uterine veins.

Ovarian pregnancy is quite rare. In these instances perhaps the fertilization occurs before the egg can be extruded from the follicle, the sperm entering the ovulation opening opportunely. Or perhaps the fertilization occurs among the fimbria or ampulla, with re-attachment to the ovary subsequently. Perhaps endometriosis of the ovary is the prime attraction for this implantation. The findings and symptoms are similar to those of tubal pregnancy. Preoperative localization of this ectopic pregnancy is impossible. When rupture occurs with intra-abdominal bleeding the treatment is excision of the involved area. This may mean the whole ovary or resection of a portion of the ovary. In very early cases resection is indicated.

Ectopic pregnancies occur in the fallopian tube in more than ninety-five per cent of cases. The position of these pregnancies in the tube affect the symptoms and course of the condition. They are as follows: interstitial, cornual, isthmal and ampullary. The interstitial pregnancy occurs in the very thick part of the fundus of the uterus as the fallopian tube is emptying into the uterine cavity. Perhaps some of these pregnancies melt into the uterine cavity and continue to term. They may progress to three or four months of age, then split out the side of the uterus and cause sudden severe hemorrhage and deep shock.

The cornual pregnancy occurs more at the very point where the fallopian tube joins the uterus. These pregnancies may grow to the age of six weeks to three months when they rupture with again severe hemorrhage and shock. The hemorrhage is more severe in these circumstances because the large blood vessels along the side of the uterus directly supply the pregnancy in this position.

The isthmal pregnancy occurs over the long part of the fallopian tube and grows to a younger age before rupture, usually no more than six weeks of age. The embryo of such a pregnancy commonly dies early, and there may be recurrent bleeding from the ruptured fallopian tube either at that point or from out the fimbriated end of the tube over a period of several weeks. Bleeding through the lumen is known as tubal abortion, occurs more slowly, and as a rule produces less dramatic symptoms.

The fourth position of the extra-uterine pregnancy is in the ampullary part of the tube, the broad and dilated portion just before it reaches the fimbria. In this area the bleeding commonly occurs out the fimbriated end as an incomplete tubal abortion. The symptoms of pain and weakness may be of longer duration than those associated with rupture of the tube. The entire products of conception may be aborted out the end of the tube under

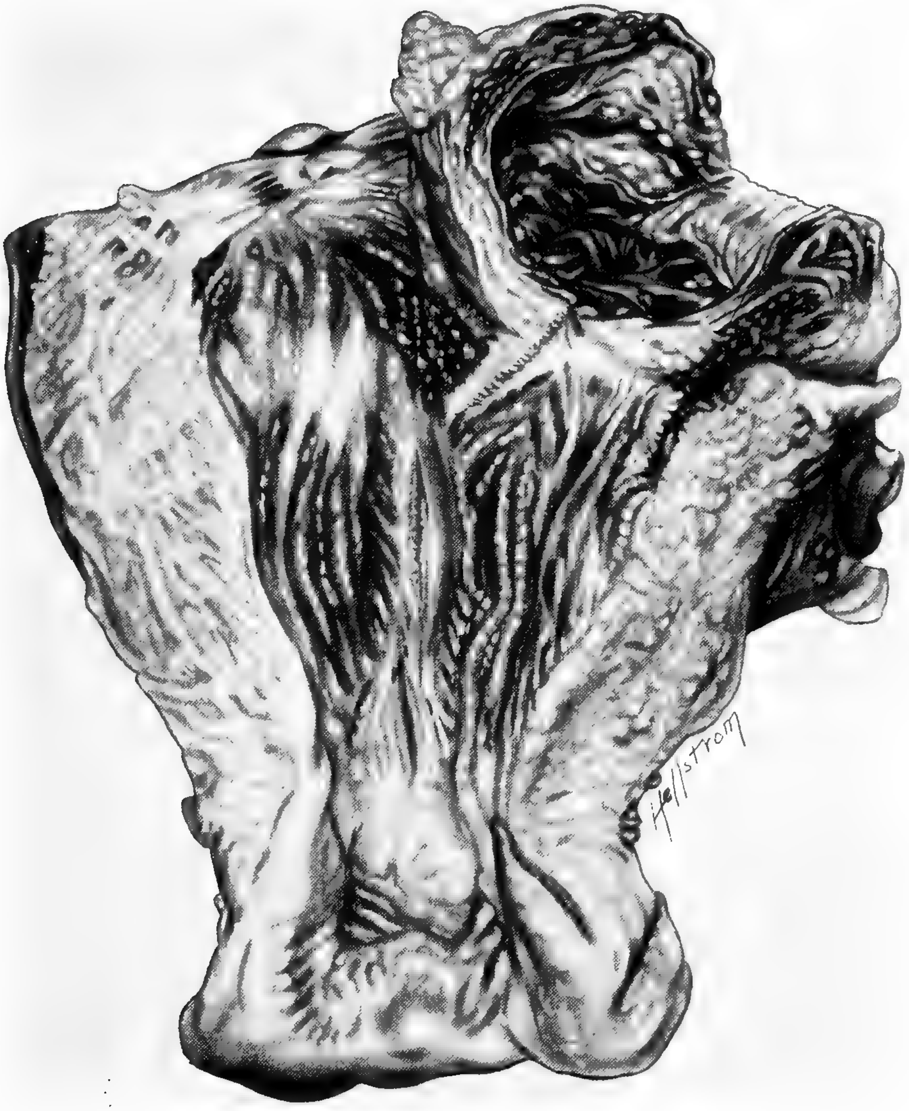


Fig. 206. Cornual pregnancy. The cavity formed in the interstitial or cornual portion of the tube was filled with blood clots. The embryo had degenerated, and the villi were largely shadows. A small perforation had been sealed over with omentum. If the villi had not ceased to function, a violent rupture would have been expected.

some circumstances along with considerable hemorrhage into the interior of the abdomen. Conceivably such bleeding might cease and the patient make a spontaneous recovery. Perforation of the tubal wall with hemorrhage and acute catastrophic findings are somewhat more frequent than tubal abortion. Secondary implantation of the extruding placenta may produce the secondary abdominal pregnancy.

The causes of tubal pregnancy are not clear. First is considered partial tubal obstruction. This includes pelvic inflammatory disease or chronic salpingitis. In the course of one's training in a charity hospital as one inspects the pelvis of those patients with tubal pregnancy, some degree of chronic salpingitis in the remaining tube is found frequently. When one sees the disease in the private practice of medicine, the inflamatory changes are rare, and one is inclined to minimize its importance. Theoretically tubal obstruction may occur from congenital abnormalities, structures, pockets, or diverticula that may occur in the tubal folds. While no one has described these with any degree of clarity, yet they remain as a possible explanation for trapping the fertilized ovum.

Another possible cause of tubal pregnancy is endometriosis in the fallopian tube. Such may be true endometriosis derived from implants of endometrium from the endometrial cavity after retrograde menstruation, or perhaps there are changes in the tubal epithelium which simulate endometrium, not enough to be called true endometriosis, but perhaps enough to attract a fertilized ovum. It is theorized that the endometrium may have a chemotactic attraction for the fertilized ovum or that it simply is necessary for implantation. Endometriosis in the fallopian tube is not uncommon and may be an important cause. This would seem a particularly good possibility as one sees cells around the placenta in the fallopian tube which are quite suggestive of decidua. If these cells do represent decidua they must have derived from endometrial changes in the tubal epithelium. This is not illogical, because the changes are frequently found and it is well understood that the entire epithelium in the upper genitalia tract has a common developmental origin from the mullerian duct.

The course of events and symptoms in the ectopic pregnancy may be chronicled as follows: Ovulation occurs fourteen days before the impending menstruation. The ovum is drawn into the fallopian tube. There it usually remains alive and potent for forty-eight hours, and it may be fertilized by a single spermatozoon. Such a fertilized egg remains in the fallopian tube for seven to nine days, gradually coming down into the endometrial cavity where it becomes attached to the surface of the endometrium. But it may become lodged in the tube by some means or other. As it becomes implanted around the ninth day of age the newly formed trophoblast begins to signal the pituitary gland by its secretion of chorionic gonadotrophin to prevent the regression of anterior lobe effects which cause menstruation. The pituitary gland continues to secrete its FSH, LH and LTH causing the corpus luteum not to atrophy but to become larger and more active in secreting increased amounts of estrogen and progesterone, which are necessary in the further implantation and development of the placenta. In the fallopian tube these placental cells, now developing into Langhans and syncytial cells, invade the small tubal folds and the wall of the fallopian tube. Sometimes the invasion is rapid and extends through the wall of the tubes to the surface quickly. Perforation of the trophoblastic cells may erode a small vessel within the fallopian tube and cause bleeding out to the end of the tube into the peritoneal cavity, or down into the endometrial cavity showing as a sign of brownish blood in the vagina. After the pregnancy is three weeks old, there may occur perforation of the tubal wall with bleeding into the abdominal cavity or perforation of vessels in the tubal mucosa with bleeding into the lumen. The first perforation of blood into the abdominal cavity usually produces sudden and severe acute abdominal pain, often so sudden as to cause a vasomotor reaction and fainting. The blood pressure may drop, the pulse become rapid and weak. Pallor is related to fainting at this time. With recovery from the syncope, the pain may continue in severe degree. The abdomen, soft at first, may become rigid with extreme tenderness, more severe in the lower abdomen. If the bleeding is slow the symptoms are milder as a rule. If the bleeding occurs as a sudden burst and clots over to stop a more active bleeding there may be recovery of composure and disappearance of symptoms. The pain may essentially entirely disappear or a slight soreness may remain. If much hemorrhage has occurred into the abdomen, varying degrees of anemia may show in the blood studies after twenty-four hours. As the free blood moves around in the abdomen, it extends up under the diaphragm and stimulates the under surface of the diaphragm. The phrenic nerve supplying the diaphragm causes a reflex pain to the top of the shoulders. This pain occurs more over the right shoulder than the left and may be unilateral or bilateral. The blood always extends into the depths of the pelvis over the surface of the rectum and produces a shooting pain through the rectum. It may cause pain on defecation or a feeling of urgency to defecate. Or the ruptured tubal pregnancy may have been covered with blood clot, partially sealed by adherent omentum and loops of intestine. The slow leaking of blood into the abdominal cavity may produce increasing anemia, and sudden repeated hemorrhages may cause severe acute pain and syncope. These encapsulated hematomas may be small or of great size.

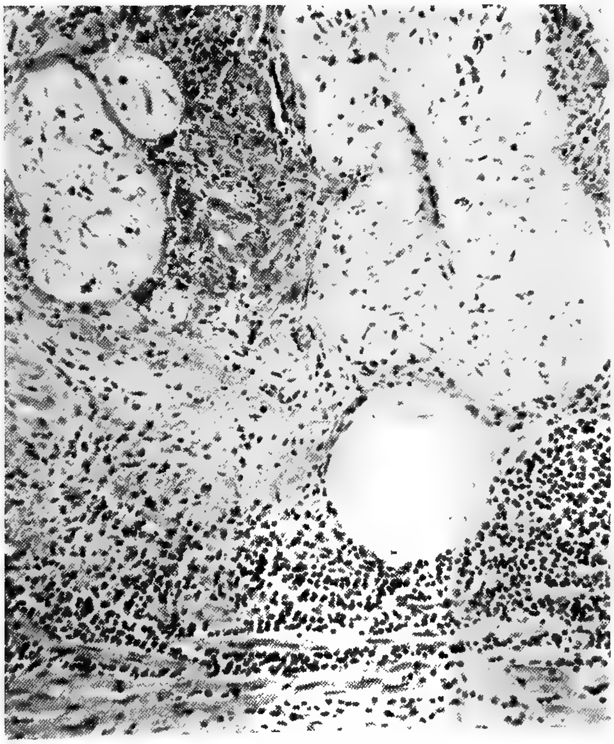


Fig. 207. Cornual pregnancy. The inferior margin shows a portion of the myometrium or tubal muscle cells in the cornu. A marked inflammation partly surrounds the largely hyalinized villi from this relatively old cornual pregnancy. (From case in Fig. 206.)

As a rule one thinks of a missed menstrual period or periods with the ectopic pregnancy and this occurs in two-thirds of the patients, but one-third may have apparent regular menstruation with irregular intermenstrual bleeding. As a rule, at the time of the first marked pain of the tubal pregnancy there follows a brownish discharge from the uterus. Whether this arises in the fallopian tube itself or in the endometrium is not clear; it probably arises in the tube. Such a brown discharge may occur two or three weeks before rupture appears. After rupture, or after supposed death of the embryo, more definite bleeding occurs from the uterine cavity. This must result from hormone deprivation because then, as a rule, the pregnancy test becomes negative, though not invariably.

The value of the pregnancy test in diagnosis is indefinite in the consideration of this disease as a whole, but in the individual case, may be of value. In fifty per cent of all cases of tubal pregnancies the pregnancy test is negative. If the test is positive one knows only that there is apparent pregnancy, but its location is not determined; it may be intrauterine or extrauterine. The intrauterine pregnancy with corpus luteum cyst and threatened abortion may be most difficult to differentiate from extrauterine pregnancy.

The first rupture may be severe and devastating, with extreme anemia and deep shock, and even fatal results. More often there are repeated episodes of severe pain and shock by the time the patient sees the physician. The picture is dramatic and characteristic, with the weak rapid pulse, very low blood pressure, the marked pallor of the mucous membranes, the slight to moderate distention of the abdomen with extreme tenderness. The absence of any profuse external bleeding is usually sufficient to clarify the probable diagnosis. Intra-abdominal hemorrhage from some other cause may give a similar syndrome, but any other type of bleeding is much less common than that from the ectopic pregnancy. Often pelvic examination is not even performed in the acute and severe case. If one does examine such a patient vaginally there may be found a brownish discharge or scant bleeding in the vaginal canal. The cervix may be soft or firm. The uterus if it could be felt, may seem slightly enlarged and soft. Perhaps a soft indefinite mass to one side of the uterus may be felt. The velvety feel of such a mass has been reiterated in the past, especially by Cullen. The cul-de-sac may feel full, recto-vaginal examination may show the fullness in the cul-de-sac more obviously, and as the fingers are pressed together the crepitation of the blood clot beneath the finger is most diagnostic of intraperitoneal hemorrhage. One may wish to place a long spinal puncture needle into the posterior cul-de-sac of the patient, pressing it in the midline behind the cervix, withdrawing blood which does not clot at a reasonable period of time. Blood in the peritoneal cavity loses its clotting mechanism to a certain degree, at least clotting is delayed as a rule. Apparently, the clots that are present have used up the clotting material present. The hemoglobin content of the blood may be very low, and the white count may be very high, even up to 20,000 or 30,000, though on the other hand the white cell count may be normal. The temperature may be normal, but sometimes extends to 100 or 101 degrees.

In the more long-standing tubal pregnancy, there may be intermittent pain over a period of several weeks and an encapsulated pelvic hematoma may be palpable, a pelvic mass that is adherent and tender. The patient may have a rather marked secondary anemia. Usually the bleeding from the uterus with an ectopic pregnancy is scant, but occasionally the bleeding is heavy and may add to the anemia present.

After the bleeding has been continuing for one or two weeks, usually in scant amount as brownish discharge, then there may be passed a cast of the uterus, a decidual cast which has the appearance of true decidua under the microscope. This may be fragmented in small pieces and may be passed as an abortion. Sometimes such a mass is quite confusing, either from seeing it or certainly from hearing the history of the patient who has seen the cast, so that one assumes the patient may have had a uterine abortion. In the more subacute or chronic case the continued bleeding may lead to curettage of the uterus. There may be found a decidual change in the endometrium, that is curetted away, but more frequently there is an interval non-secretory endometrium, the decidua all having been cast away or washed away by the uterine bleeding. These should have negative pregnancy tests, as the hormones evidently have regressed. The regrowth of interval non-secretory endometrium is not illuminating. There may be some degree of chronic endometritis present as indicated by the presence of lymphocytes, and particularly plasma cells.

The needling of the cul-de-sac has been highly recommended by many as a diagnostic procedure, particularly by the New Orleans group. In the very acute case undoubtedly it is not necessary. In the less serious degree of bleeding the aspiration of blood undoubtedly is helpful at times. In the chronic case perhaps it may be of value. We speak of the chronic case as being a frequent one. We should say that the subacute case is a frequent one and the chronic case most uncommon.

Ectopic pregnancy or extra-uterine pregnancy is one of the most severe and serious acute emergencies that occurs in the practice of medicine. Certainly none is more important in the field of gynecology. The understanding of symptomatology and physical findings is of greatest importance to every physician. One may look back through the years at individual case histories; forty years ago the author's father, a general practitioner of considerable ability, lost an attractive young mother who

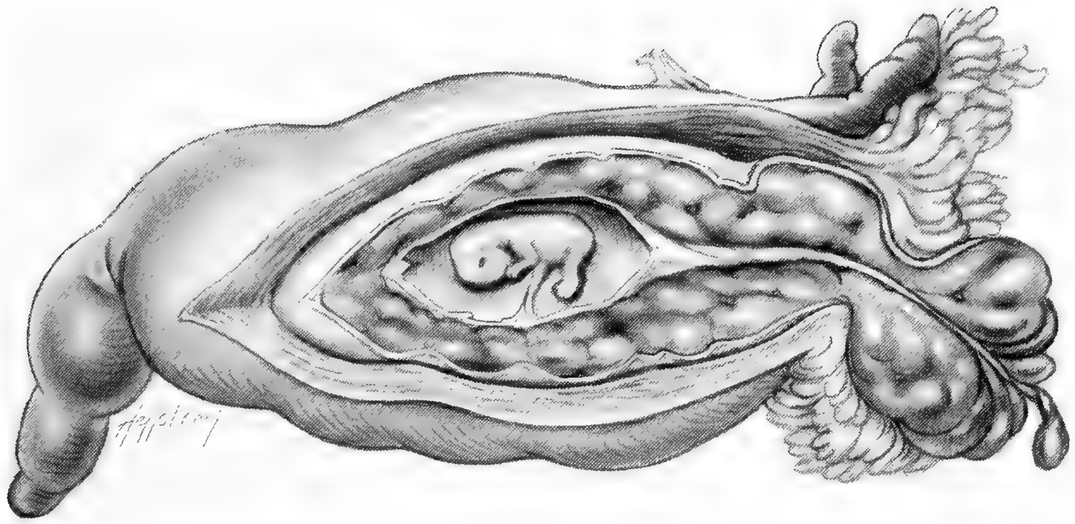


Fig. 208. Tubal pregnancy left, with tubal abortion. Bleeding into the abdomen is slower than with rupture; also less severe pain is associated.

had missed a menstrual period, developed pain in the abdomen and pallor which increased gradually, and then became suddenly most severe with deep shock and death. At that time this excellent physician did not understand the course of events. Some years later, after his son had finished his third year in medical school and in discussing cases and symptoms, the father suddenly realized what the diagnosis must have been, that of a ruptured extra-uterine pregnancy. Another dramatic case is that of an eighteen year old young woman, engaged to be married, who was working with her fiance in the apartment in which they subsequently would live, who developed pain in the abdomen and fainted. This occurred during a regular menstrual period. She was returned to her home, and the pains were of moderate degree during the evening. Her physician was called who suggested that her parents bring her to the hospital for his examination where laboratory work might be performed, but she improved rapidly and decided not to visit the outpatient department of the hospital. The next several days she complained of various pains and weakness. Finally one week later, her mother went to waken her in the morning and found her deceased. Autopsy showed a ruptured tubal pregnancy. This tragedy seems impossible to occur in 1959, a case in which one would never suspect pregnancy, a case not seen by a physician. The third case illustrates a further point. A patient was admitted to the hospital in good condition with missed menstrual period, moderate pain in the side, and a soft velvety mass which was readily palpable. There was no obvious severe bleeding. The pre-operative diagnosis was probable extra-uterine pregnancy. The patient was scheduled for surgery the following morning. At midnight the night nurse in her rounds found the patient dead in bed. Probably pelvic examinations made the intra-abdominal

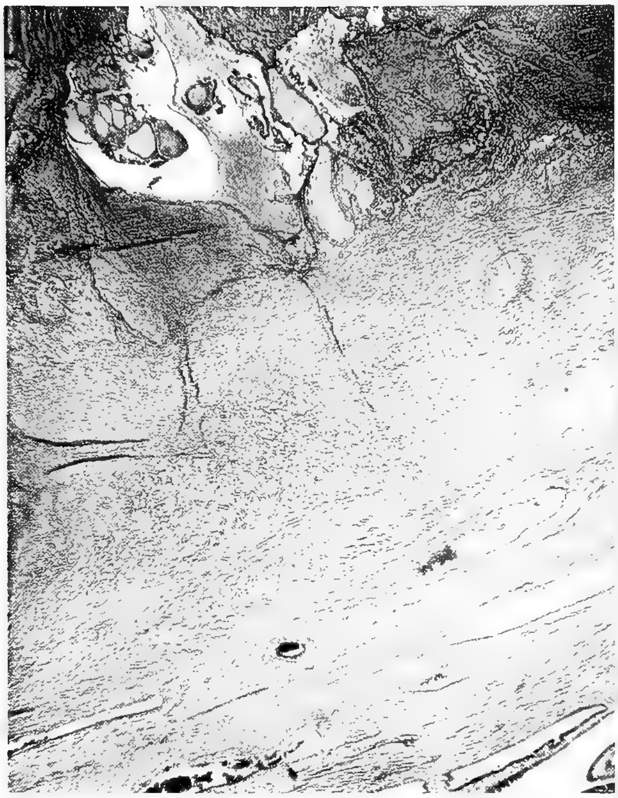


Fig. 209. Tubal pregnancy. Inferiorly a portion of the tubal wall is seen. The large midportion is made up of blood and blood clot within which are seen chorionic villi. These are young villi because they have no blood vessels in the center.

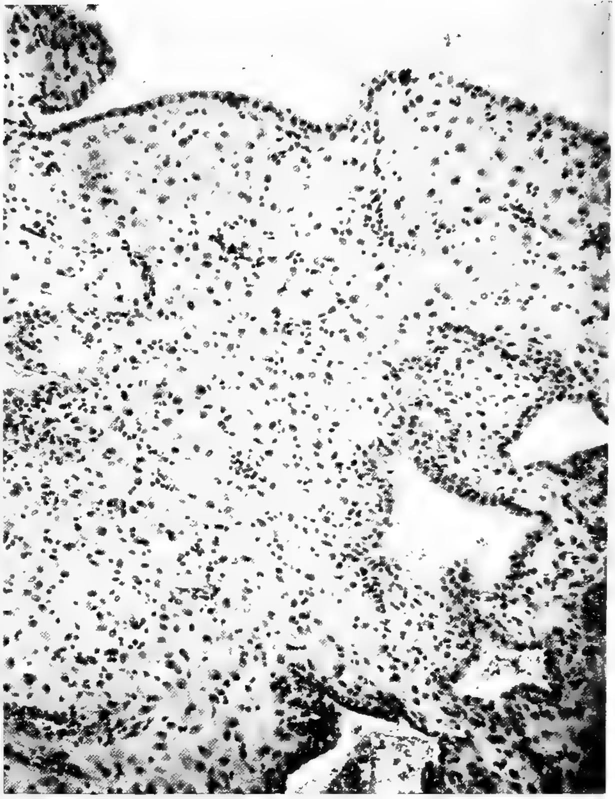


Fig. 210. Decidual cast in case with tubal pregnancy. This obvious decidual change in the zona compacta of the endometrium, and the areas of the spongiosa with endometrial glands exhausted of their glycogen, are characteristic of decidua. However, there is increased polymorphonuclear cells, and the stromal cells appear more shrunken and darker than normal. This is a portion of a complete cast of the lining of the uterus passed during the clinical course of the ectopic pregnancy.

bleeding occur more rapidly, although the result may have been a spontaneous one.

In recent years the culdoscope has been introduced by Decker and has become a popular instrument. The culdoscope is a form of a cystoscope which is introduced into the posterior cul-de-sac through the vagina with the patient in the knee-chest position. The vagina balloons out and becomes thin and stretched in this position. Introduction of the cannula allows air to rush into the abdomen so that the intestines fall away from the pelvic organs. This method of direct visualization is useful for diagnosis of various diseases in the pelvis. It is particularly valuable for the diagnosis of unruptured tubal pregnancy, and of some value in the case with early rupture with relatively small amount of blood in the abdomen. It would certainly seem impossible to distinguish the true nature of the intra-abdominal pathology if there is a large amount of blood in the abdomen, as with the ruptured ectopic pregnancy with severe bleeding. The hesitancy in accepting the principle of culdoscopy is heightened by the possibility of injury to the viscera in the introduction of the instrument. In its introduction a dagger-like sharp trocar is pressed through the posterior fornix of the vagina into the posterior cul-de-sac. If the intestine should be adherent, the rectum or sigmoid or small intestine, in the cul-de-sac or to the back of the uterus, then injury to the bowel would be certain. If the cul-de-sac is unusually shortened between the cervix and rectum, the possibility of injury would be greatly increased. And this must be true in a certain number of cases, as extra-peritoneal introduction of the trocar has happened in many instances, evidently extending up alongside of the rectum beneath the peritoneum. In other cases every one with experience with the instrument has undoubtedly seen, or known of, or produced injury of the intestines, particularly the rectum. Many have withdrawn the instrument and have hoped that the perforation was extra-peritoneal and have had healing with little difficulty or after the formation of an abscess which drained spontaneously, was incised by colpotomy, or absorbed after antibiotic therapy. On the other hand, there have been serious reactions requiring laparotomy, suture of the perforation and treatment of the peritonitis and ileus. That a fatality can occur with this procedure is undoubtedly possible and undoubtedly has occurred. It is our opinion that the culdoscope in its present development is not for a general use.

Another word about culdocentesis which has been popularly used in the diagnosis of ectopic pregnancy, or at least in the diagnosis of intra-abdominal bleeding. A relatively large spinal puncture needle of eighteen gauge is inserted into the posterior fornix of the vagina and pressed through the cul-de-sac into the abdominal cavity. If blood is obtained it may come from the venous plexus in the wall between the peritoneum and the vagina. But such blood clots within three or four minutes. Intra-abdominal blood usually is partially clotted, which uses up the clotting factors so that the remaining fluid blood does not clot. If blood is withdrawn and does not clot within ten minutes, one assumes there is true intra-abdominal extravasation of blood. The most frequent cause in women is ectopic pregnancy. Though rupture of viscera, cysts of ovaries or varices of the mesentery and retroperitoneal vessels may explain such hemorrhage. This needle may perforate the intestinal tract, as evidenced by the withdrawal of odorous gas from the intestine; as a rule there is no serious sequela from this perforation. Yet one cannot believe that it is entirely innocuous, as some degree of inflammation and local peritonitis must occur, which might be sufficient to cause a mild salpingitis with closure of the lumen of the fallopian tube. If the ectopic pregnancy is unruptured, obviously the needle will not obtain free blood. The unruptured ectopic pregnancy is most difficult of diagnosis; usually many are suspected before one is confirmed. On the other hand, sometimes the tap is negative, possibly because free blood is not present in large amounts and has not seeped into the cul-de-sac but remains between loops of bowel, because the needle enters a blood clot, or because the needle extends into an extraperitoneal area. A positive finding is more important than a negative one. In the hands of some the accuracy is said to be very great, but in others less enthusiastic is undoubtedly smaller. It remains a valuable diagnostic method but generally is corroborative of an opinion based on clinical judgment, from correlating the history of the patient with the physical findings.

Every physician probably constantly has one or two or more cases under observation that might possibly have an ectopic pregnancy, and it is by observation and examination at invervals (weekly or as judged necessary) that the diagnosis clarifies itself. It is true that once a diagnosis is made operation should be prompt, not as a strict emergency, but as within a reasonable time. The diagnosis of the unruptured tubal pregnancy will always remain difficult and one that can be readily in error. We are inclined ordinarily not to operate for the possibility of an unruptured tubal pregnancy, but to observe the patient until there is some degree of leakage of blood into the peritoneal cavity that will make the diagnosis more obvious.

The *treatment* of ectopic pregnancy is surgical. The difficulties are mainly in the diagnosis and sometimes in the condition of the patient. As a rule surgical excision is indicated when the diagnosis is made, particularly if there is rupture. As mentioned above the unruptured ectopic pregnancy is rarely discovered. It may be suspected many times for every one that proves to have this true diagnosis, but if there is evidence of rupture and free blood in the abdomen as shown by obtaining blood with the culdocentesis needle or by shock and pallor, then operation is urgently indicated, as the bleeding may progress to a fatal outcome from exsanguination into the abdominal cavity. Although such an outcome is rarely seen today it remains as a definite possibility in every case. If the patient is in good condition the surgery may progress even without the preparation of blood transfusions, and low spinal anesthesia and intravenous pentothal may be used. But if the patient is in shock one would always prefer to have available one or two pints of matched blood, and probably would not use spinal anesthesia, but rather inhalation and intravenous anesthesia with supporting methods. A midline incision opens the abdomen. As a rule a large amount of dark blood wells up out of the abdomen. The retractor is quickly inserted, and the hand, usually the left hand if one stands on the right side of the patient, is inserted into the depths of the pelvis. Quickly blood clots may be evacuated from the abdomen, and by touch one determines which side is involved in the pregnancy. As a rule, this pregnancy involves a fallopian tube which may be enlarged to the size of a cigar or much larger, 5 or 6 cm. in diameter including the localized blood clots. Such a mass rapidly is raised out of the pelvis. If possible, one separates the ovary which is often imbedded within the blood clot and light adhesions developing from reaction to the tubal pregnancy. The separation from the ovary, so that it may be conserved usually is simple, if one thinks of it. Kelly clamps may be placed alongside the tube, after which the tube is excised, removing the cornu in a wedge-shaped manner. The cornu is closed over with a figure-of-eight suture, the various clamps along the broad ligament are ligated with interrupted suture. The distal portion of the broad ligament is usually sutured just under the cornu of the uterus and the round ligament is drawn over the cornu on this side alone to afford suspension and peritonization. Blood clots are scooped out of the abdomen as they are found, but no effort is made to remove all the free liquid blood, as it absorbs and may be of value to the patient. It is better to remove the clots. The depth of the pelvis is quickly inspected for any further bleeding, and if there have been no adhesions torn one would not expect much. The sigmoid is draped over the operative site, omentum drawn down and the abdomen closed rapidly in layers. Such an operation occasionally may be performed in ten or fifteen minutes, and speed is of the great importance when the patient is in shock.

Sixty years ago Hunter Robb carried out a series of experiments on dogs by cutting the uterine and ovarian arteries and then closing the abdomens. He found that these dogs did not die from intraperitoneal hemorrhage. It was his belief, and that of many others following his time, that the patient in shock from hemorrhage from an ectopic pregnancy should not have immediate operation until the shock had subsided and the patient had improved sufficiently to make the operation safer. As a result of this expectant and supportive treatment apparently many patients had a fatal outcome. Following this, the general opinion developed that the patient was better treated by immediate operation as soon as she was seen. Intravenous glucose is used to elevate the blood pressure from forty mm. to sixty to seventy mm. or so, systolic, after which the flow of glucose is decreased to prevent more rapid intra-abdominal bleeding, but simply to maintain a state of conscious-

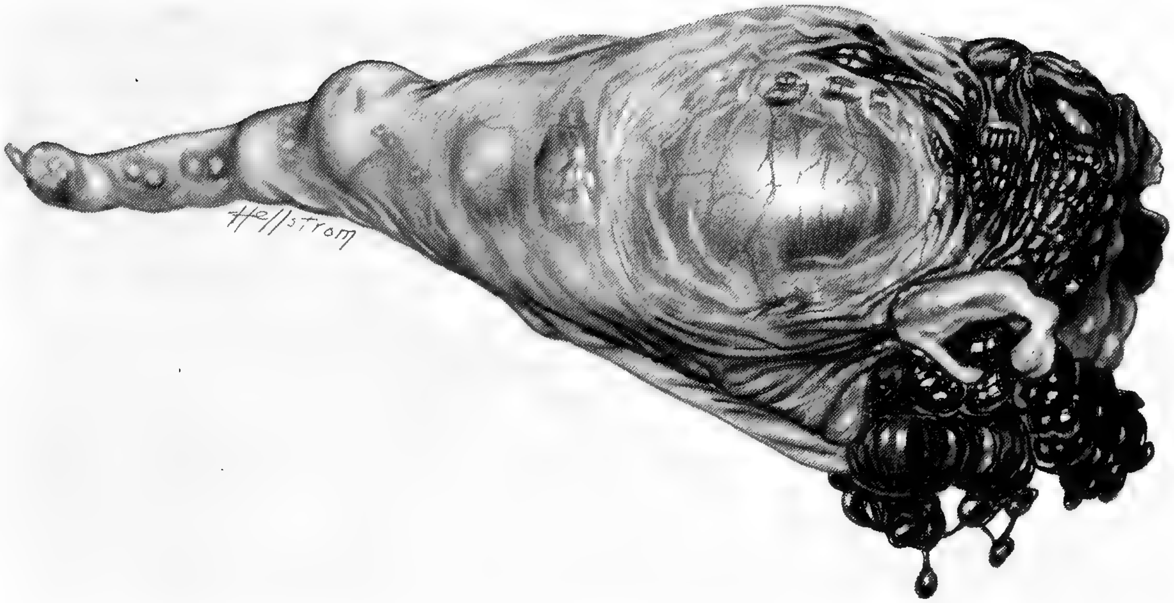


Fig. 211. Tubal pregnancy ruptured, with extrusion of imperfectly formed embryo. Clots remain in the ruptured tube. A large amount of free blood and clots were present.

ness and sufficient blood flow to the brain to prevent serious damage. As quickly as possible the operation is performed opening the abdomen. It has long been known that as soon as a hemostatic clamp can be applied to the blood vessels beneath the fallopian tube which is hemorrhaging there is immediate improvement in the status of the pulse and blood pressure of the patient. As soon as this clamp is applied intravenous fluids are rapidly introduced into the patient to help elevate the blood pressure to a more normal level. Blood transfusions are administered as available and as necessary.

Fatality does occur and will continue to occur with the rapid surgical approach as a choice for treatment, particularly because some patients are seen in complete extremis and time has run out on them, not allowing an operative procedure. In addition there is the slight shock of the operation itself, though this is rarely of importance compared with that of the blood loss. Since blood transfusions have become so expeditiously prepared and given in the last ten years or more, obviously one would prefer to have blood available. When a blood bank is available and rapid typing and matching may be performed, the operation rarely need be delayed. But if no blood is available in the blood bank or from immediate available donors, it would seem as a rule that surgery should proceed even without transfusion. This may require courage on the part of the operating surgeon to make this decision as it is always easier to wait, but undoubtedly some patients succumb to a waiting procedure. Rapid and accurate surgery is always beneficial to recovery from shock. Through the years a few gynecological surgeons have advised the use of retransfusion of blood removed from the peritoneal cavity. This has been used similarly with hemorrhage into the pericardial cavity or in the pleura cavity. Also auto-transfusion has even been used for hermorrhage into the abdominal cavity after gunshot wounds which may have perforated the intestine and allowed fecal material to become contaminated in the free blood, often without ill effect. On the other hand there are well recorded cases of serious reactions and even fatal results from such transfusions. Under emergency situations autotransfusion may be used occasionally, passing it through a strainer into a transfusion set.

As a rule at the time of operation for ectopic pregnancy, which ordinarily means a ruptured tubal pregnancy, it has been long established that further elective surgery is not performed at the same time; that is, the uterus, opposite tube and ovary, and the appendix are not removed at the same time as removal of the offending fallopian tube. Particularly important is the patient's condition of shock or blood loss. Since poor results have followed additional surgery in patients in critical condition it is generally accepted that additional surgery should not be performed in any case of ectopic pregnancy. This is not always true. If there is relatively little abdominal bleeding and if the patient is in excellent condition and if blood replacement is available, often there is no reason that any necessary surgery, not too time consuming and not too complicated, should not be performed. This particularly refers to appendectomy. There is a difference of opinion regarding this point.

Ectopic pregnancy remains one of the great emergencies of gynecology. Always to be kept in mind are its many manifestations, and most bizaare and unexpected symptoms. As with appendicitis it may fool the expert.

CARCINOMA OF THE FALLOPIAN TUBE

Carcinoma of the fallopian tube is a rarely occurring tumor. Relatively few will be seen in any one experience. This papillary adenocarcinoma occurs between forty-five years and old age; occasionally, it may be found in younger women. As with any malignancy, it may occur in the very elderly.

The enlarged, sealed fallopian tube often

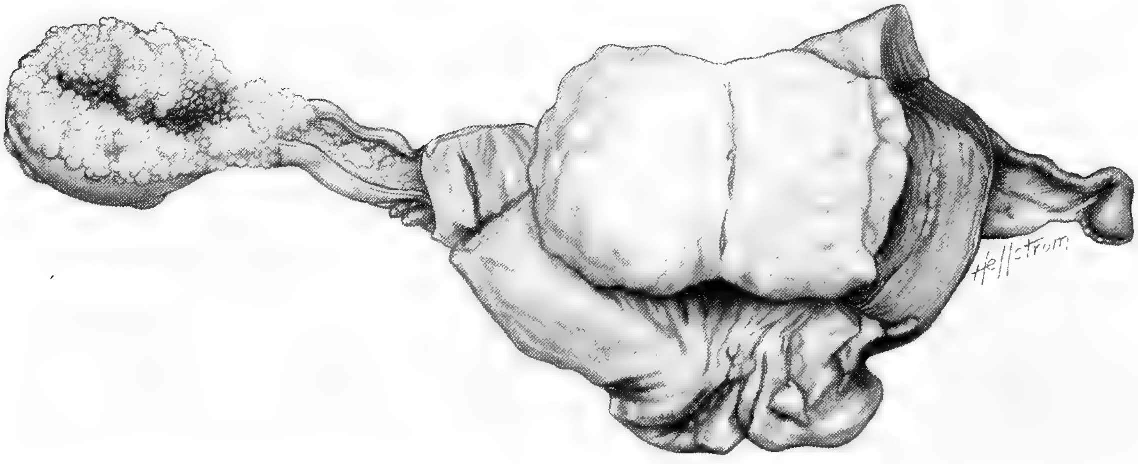


Fig. 212. Papillary adenocarcinoma of left fallopian tube, which has been opened longitudinally. The surface was smooth and fimbriated end characteristically sealed over. The submucous myoma was unrelated.

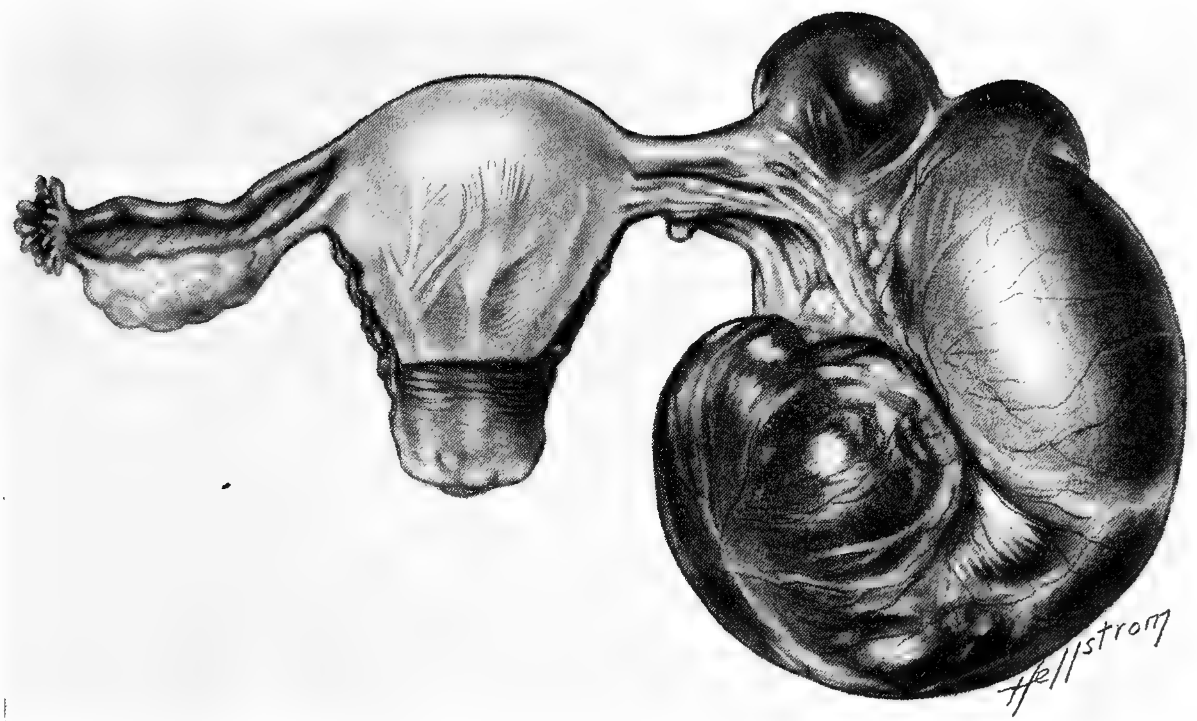


Fig. 213. Carcinoma of right fallopian tube, which appears as hematosalpinx. Patient was 70 years old, with scant bleeding from vagina. Interior of tube was largely filled with adenocarcinoma, grade IV.

is thought to represent pelvic inflammatory disease with hydrosalpinx. Or this characteristic appearance may extend from the slightly enlarged hydrosalpinx to a relatively large tubo-ovarian cystic mass. The color varies from pale pink or white to a dark purple when old blood fills the lumen. Within such a tube there may be clear fluid, or blood tinged fluid, more frequently the latter, and only a small amount of papillary carcinoma around the interior of the tube. On the other hand, the tube though only slightly enlarged may be filled with papillary adenocarcinoma. As a rule, the distal end is closed, the cause of which is not clear; this gives rise to the thought that the tumor may be preceded by chronic salpingitis. Less frequently the distal end is patent into the peritoneal cavity.

The adenocarcinoma is similar to that occurring in the endometrial cavity. That it may arise from tubal endometriosis remains a possibility. That it may be produced by chronic salpingitis or tuberculosis seems unlikely. Probably, this tumor arises from those cells normally present in the fallopian tube. It is insidious in development, difficult of diagnosis, and commonly recurs after surgery.

Secondary carcinoma of the fallopian tube occurs not infrequently from extensions and metastasis from carcinoma of the endometrium. It is thought that metastasis from the endometrium to the ovary occurs by way of the lymphatics along the fallopian tube. Not infrequently small implants may be seen in the endosalpinx, from endometrial tumors. Similarly, carcinomas of the ovary may extend or metastasize into the fallopian tube on their way along the lymphatics, which extend from one side to the other, crossing the fundus of the uterus. These tumors from the ovary are most variable in type. Conceivably, other tumors in the body may metastasize to the fallopian tube.

The *symptoms* of this disease are mild and treacherous. Ordinarily, the patient complains of a scant brownish discharge or scant bleed-

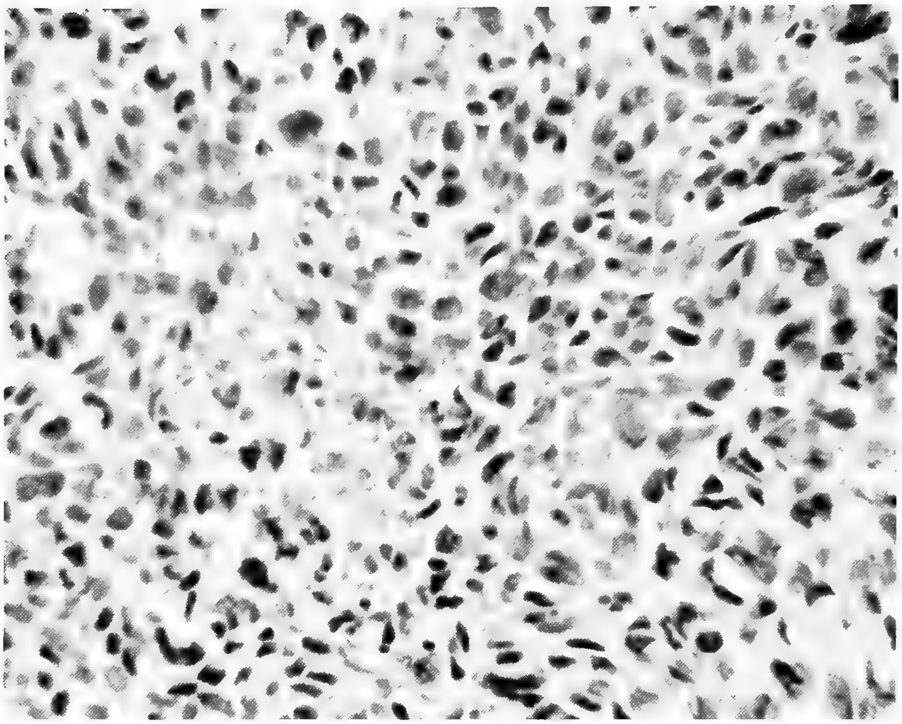


Fig. 214. Carcinoma of the fallopian tube, grade IV. The epithelial cells which arose from the tubal epithelium show a solid appearance with marked variation in the nuclei and numerous mitoses. The more frequent finding in carcinoma of the fallopian tube is the more differentiated papillary adenocarcinoma, with glands back to back and piled up epithelial cells. (From case in Fig. 213.)

ing from the uterus, of intermenstrual character or postmenopausal. There may be slight discomfort in one or both lower quadrants of the abdomen; such discomfort may be overlooked or ignored by the patient. At the time of examination one may palpate a soft cystic mass to the side of the uterus, such as occurs with the hydrosalpinx, a sausage-shaped mass or a retort—shaped cystic mass, suggestive of the tubo-ovarian inflammatory cyst. On the other hand the mass may not be palpable because the tube is not sufficiently enlarged, or because it is soft and does not give enough resistance to be felt. Because of the intermenstrual bleeding or postmenopausal bleeding, one may curette the uterus, obtain benign endometrium, and miss the tubal carcinoma that may be present. In recent years, several instances of carcinoma of the fallopian tubes have been reported diagnosed by the Papanicolaou cytology studies of cervical smears. The cells represent cancer cells extruded into the uterine cavity and out the cervix from the tubal tumor. When curettings and cervical conization are negative in the instance of positive cervical smears, the possibility of carcinoma of the tube or ovary must be entertained. The scant bleeding may arise from the papillary tumor itself and seep into the uterine cavity.

If one realizes the correct diagnosis at the time of operation, the preferred treatment is excision of the entire uterus and cervix and both tubes and ovaries. Sometimes one may remove only one fallopian tube, the diagnosis being made later in the pathology laboratory. In such circumstances, as a rule, re-operation should be performed, with removal of the uterus, remaining tube and both ovaries. Irradiation therapy is of little value, whether immediately after surgery or with later recurrences. The carcinoma may spread through the surface of the fallopian tube to the adjoining peritoneum, may appear or metastasize in the omentum, liver or other organs. At times this growth extends into the edometrial cavity, and vice versa. An endometrial carcinoma may extend along the mucosa of the fallopian tubes.

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CHAPTER IX

Diseases of the Ovary

There are four important clinical considerations related to diseases of the ovary. The first includes *functional diseases,* produced by abnormalities in the secretion of the pituitary and ovarian hormones. These are the functional cysts of follicular and luteal origin, later to be separated from the neoplasms. The second group includes *inflammatory diseases* of the ovary, in the main, secondary to salpingitis. The third encompasses a separate consideration of *endometriosis,* now particularly involving the ovary in this discussion. The fourth includes *tumors* of the ovary, which may be *benign or malignant,* functional enlargements or true neoplasms, and which require consideration of conservative (observation) or operative treatment. In the latter, a large variety of extraordinary new growths occur and they will be discussed individually, though not in minute detail. The more important point is not the exact type of tumor that the patient may have, but the proper disposition and follow-up of the case. Usually it is impossible to determine the precise type of tumor preoperatively.

FUNCTIONAL DISEASES AND HISTOLOGY OF THE OVARY

A review of the histology of the ovary reveals that it is covered with a single layer of cuboidal epithelium, called the germinal epithelium. Such epithelium arises from the very young mass of germinal cells before there is differentiation into any other elements in the ovary. The term does not mean that the cells arise from the particular germ cells which form the ova or from the ovum itself. Evidently, the predecessor of each gives rise to the germinal epithelium on the one hand and the germ cells (ova) on the other. The ovary is the only organ in either sex that is inside the peritoneal cavity, all of the other organs being covered by flattened mesothelium of the peritoneum. The germinal epithelium dips down into the convolutions of the ovary, and may be squeezed off at various points to form minute cystic gland-like spaces in the cortex of the ovary. The cortex of the ovary is composed of a peculiar connective tissue which has unknown functions, but may secrete estrogenic hormone.

In the Stein-Leventhal syndrome the superficial stroma becomes markedly coarsened and fibrotic, and forms a rather separate layer around the surface of the ovary. This Stein-Leventhal syndrome includes the presence of the enlarged white ovary with thick, smooth, glazed "capsule," with multiple small follicular cysts, termed microfollicular, and is associated with amenorrhea, or oligomenorrhea, hirsutism of slight to moderate degree, slight obesity and sterility. The originators of the concept of this syndrome have treated these patients with wedge-resection of the ovary, removing one-fourth or one-half of each ovary, and approximating the edges with catgut suture. The results are considered to be very satisfactory, in properly selected cases. Possibly too many patients are having this diagnosis and operative procedure without improvement in menstrual function or fertility.

In certain conditions, as adenocarcinoma of

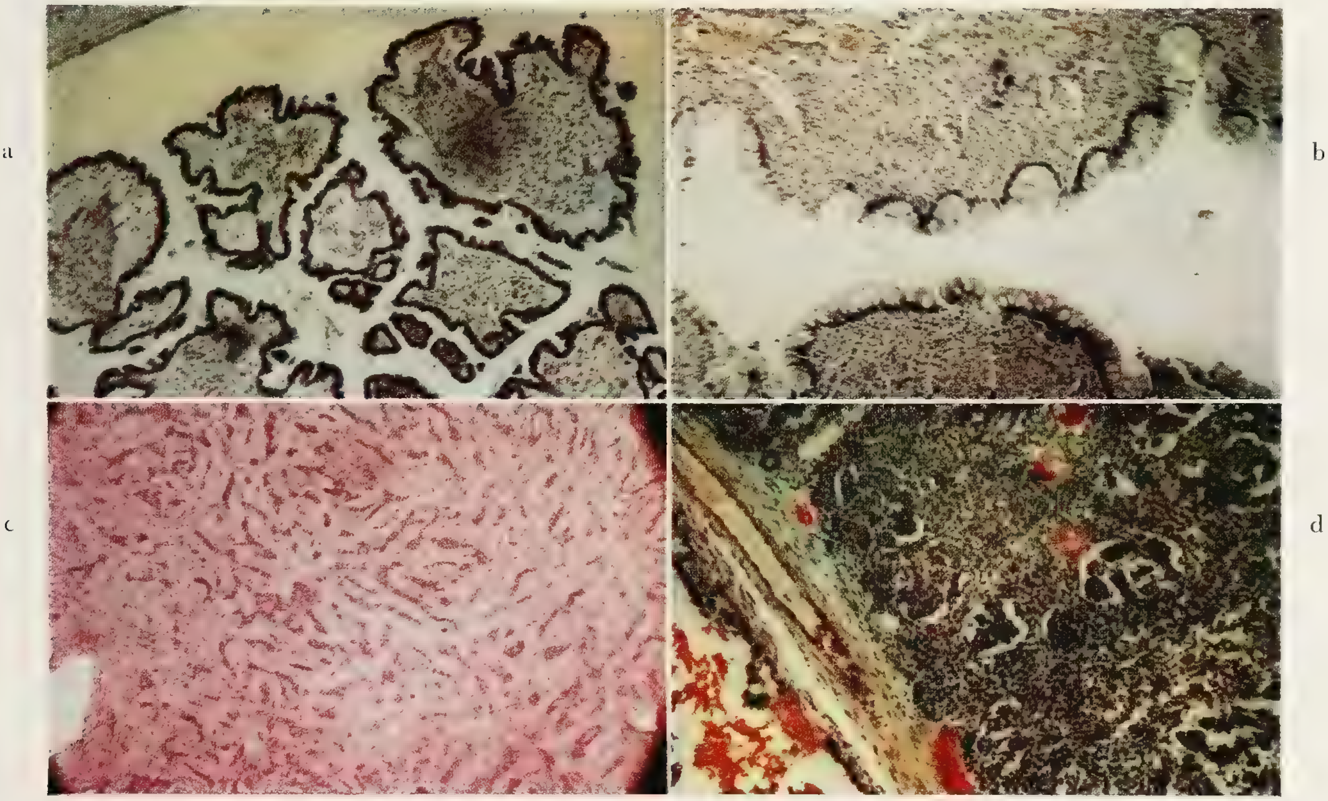


PLATE V

a. Papillary serous cysto-adenoma. The papillary projections are covered essentially by one layer of epithelial cells having a ragged cytoplasm. There is very slight piling up of cells. In other areas, this tumor may show malignant change.

b. Pseudomucinous cystadenoma. The lining cells form a single layer, very tall, with basal nuclei. The cytoplasm of the cells is distended with mucin.

c. Granulosal cell tumor. This somewhat unusual fibroma-like tumor has strands and cords of small bluish-staining granulosal cells.

d. Mesonephroma. This embryonic tumor forms tufts reminiscent of glomeruli. Cords of small dark cells and slight tubule formations make up the background.

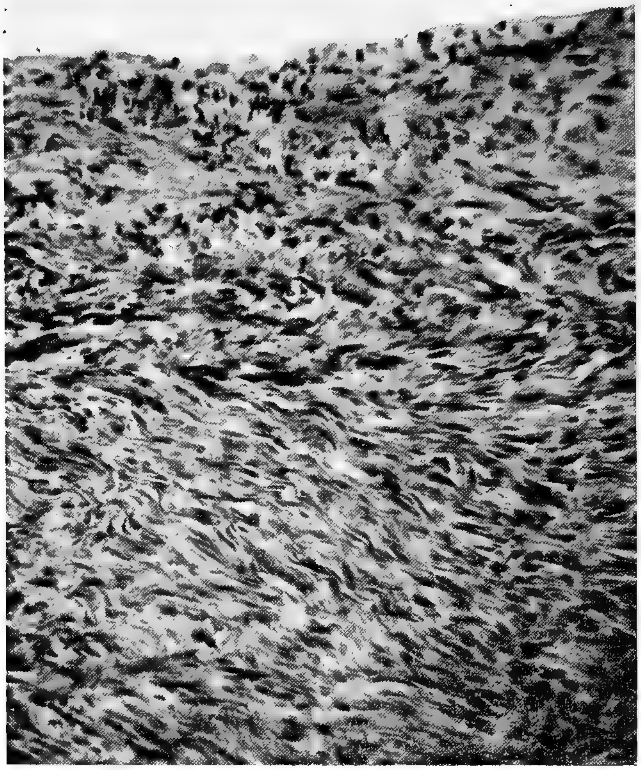


Fig. 215. Atrophic ovary or the senile ovary showing a small area of germinal epithelium on the surface. Often the germinal epithelium is brushed away in the handling of the ovary or its fixation. The stroma here is quite fibrous and the cells are densely packed together. Essentially no epithelial elements are seen within the stroma, the ova and the follicles having disappeared.

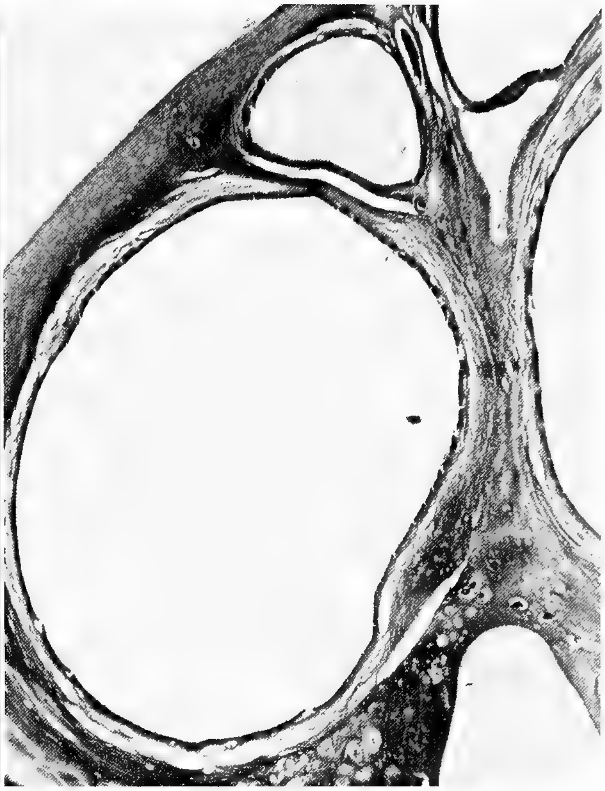


Fig. 216. Multiple follicular cysts of the ovary. The follicles are quite distended with their follicular fluid, being lined by several layers of granulosal cells. The shrinkage around the follicles is due to the fixation. This patient probably had hyperestrogenism.

the endometrium and breast, and postmenopausal endometrial hyperplasia, stromal hyperplasia has been noted in the cortex of the ovary by a few observers. The importance of this finding is not clear. Some have felt that it means continued ovarian function in the postmenopausal patient with estrogen secretion, which may stimulate the endometrium; others have discounted these findings and this theory.

Within the cortex of the young ovary there are some 400,000 primoridal ova, surrounded by a single layer of granulosal cells. Of these numerous primordial ova only 300 or 400 are destined to be extruded from their follicles into the peritoneal cavity, for possible travel into the fallopian tubes and occasional fertilization. The remainder of the primordial follicles apparently are used as supporting follicles, as certain ones in each cycle produce estrogen in increasing amount up to the time of menstruation. By the time of the menopause, very few ova can be found in the cortex of the ovary. During the normal menstrual cycle one follicle is to be the primary or dominant follicle of that cycle, destined to grow to a diameter of two or three cm., bulging up from the surface of the ovary, with marked proliferation of the granulosal cells, both around the interior of the follicle and heaping up around the ovum (the cumulus oophorus). Surrounding the follicles the connective tissue-like cells, called thecal cells, become larger and are some four to eight layers thick. The theca interna shows definite changes with the cycle of the pituitary hor-

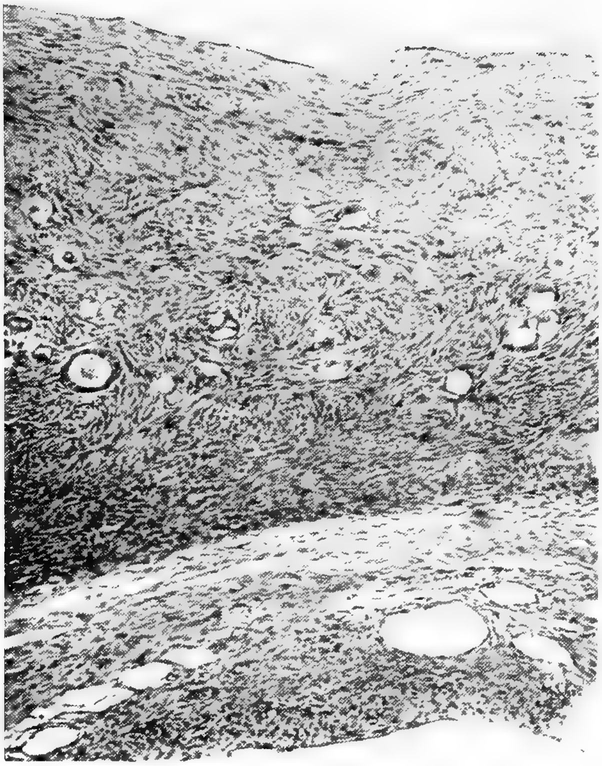


Fig. 217. Stein-Levinthal ovary. The thick "capsule" represents a fibrous appearing change in the superficial layer of the stroma of the ovarian cortex. The germinal layer is normal. Beneath the eosinophilic superficial layer are prinordial follicles with their ova. Deep to these are micro-follicular cysts, having a prominent thecal layer.

mones, while the theca externa appears more as a thin layer of ovarian stroma, showing little change.

Small graffian follicle cysts are present in almost all normal ovaries. That is, nearly every ovary contains two, three, four or five small cysts, up to one cm. or more in size. We have the concept of several graffian follicles being stimulated at the same time as the primary follicle containing the dominant ovum of that particular cycle is being stimulated. The several assistant follicles appear to secrete estrogen to support the purposes of estrogenic function. Also, it is thought that these follicles atrophy, become atretic, and disappear at the end of this particular cycle. As to whether or not the small follicle cysts, so frequently seen incidentally in the otherwise normally functioning and ovulating ovary, are entirely of this ephemeral type or whether they may remain for several months, is unknown, because no one can observe a particular small follicular cyst at repeated intervals through a period of months. It does appear, in the pathological situation of metrorrhagia and endometrial hyperplasia, that the graffian follicle cysts, which characteristically form in the ovary, are sometimes no more numerous than are seen under normal circumstances; at other times, they become numerous, prominent, enlarged to two or three cm. in diameter, and may cause together a palpable, cystic enlargement of the ovary. It would seem, under the apparently continuously stimulating effect of FSH from the pituitary gland, that these follicle cysts must remain for a period of weeks or months, before regressing, and then, apparently only when the hyperstimulation from follicle stimulating hormone diminishes, by some mechanism unknown.

In the clinical examination of the patient, an ovary may feel enlarged to two or three times normal size, due to the presence of small follicular cysts, which are usually multiple, and when added together, cause the seemingly diffuse enlargement of the ovary. If the patient has a normal cycle, such an enlargement may disappear in the following month. Since the follicles first appear before ovulation, the enlargement due to follicular cysts would be more obvious before the mid-cycle, and while they may persist into the latter half of this cycle, enlargement after the time of ovulation more likely would be due to a corpus luteum cyst.

The enlarged cystic ovary or ovaries that are associated with metrorrhagia, and consequently with endometrial hyperplasia or interval non-secretory endometrium (which may be a phase of endometrial hyperplasia) usually vary little during a few weeks of observation, unless the abnormal function is corrected, or corrects itself. But during long continued observation of the patient with metrorrhagia and endometrial hyperplasia, the size of ovaries often vary considerably from time to time. It has not been determined whether a particular follicle cyst, that once forms, remains through the course of this functional disease, though it is assumed that it does. Atresia may follow at any time if there is a change in the stimulating effect of the pituitary gland.

The micro-follicular cysts have been mentioned above under a discussion of the Stein-Leventhal syndrome. As to whether these cysts are small because they are unable to penetrate through the thickened cortex of the ovary in this condition, or whether they have not received sufficient stimulation from the pituitary gland to carry them to their usual development, has not been clarified. Marked hyperplasia of the theca interna cells in the walls of atretic follicles is frequent in this syndrome. Similar micro-cysts are found scattered through normal ovaries and ordinarily are considered of no importance, again usually assumed to be associated with a particular cycle and later to disappear by atresia.

The occurrence and clinical syndromes associated with follicular cysts are discussed under the chapter on menstrual dysfunction. The dominant follicle of a particular cycle may develop up to the time of ovulation and may not be stimulated to ovulation, as is well known. Such a follicle, with its smaller bridesmaids, progresses until the stimulus of the FSH is removed, when it becomes inactive and regresses, to disappear in atresia. Some follicle cysts that are well formed seem "burned out", are lined by only a few atrophic granulosal cells, and perhaps may remain in the ovary for long periods of time. It does not appear that any large, cystic tumor may ever develop from the adult graffian follicle, or from the adult granulosal cells.

When the trigger of ovulation, the mechanism of which is not known exactly, is tripped, the follicle first opens, the liquor folliculi extrudes out of the opening, and the egg is expressed into the peritoneal cavity. Apparently the fimbriae of the fallopian tube are drawn toward the point of ovulation by chemotaxis or electrical potential, where the action of their cilia seem to aid in drawing the egg into the fallopian tube. After ovulation has occurred, there is extruded into the interior of the follicle fresh blood, and the follicle is almost instantly transformed into a corpus luteum. The granulosal cells rapidly begin to enlarge, take on a yellowish color due to the manufacture of a fatty material in their interior. As these cells become tremendously larger, they press out into the center of the hematoma in festoons, producing the characteristic wavy appearance of the thick yellow border of the corpus luteum. The thecal cells also become rather large, paler, and contain fat, though to a less degree than the luteal cells. The blood in the interior of the corpus luteum (all are hematomas to begin with) commonly is absorbed, and there remains a small amount of clear fluid within the cavity. In a generous percentage of corpora lutea, the interior forms an increased amount of fluid, so that the yellow body protrudes from the surface of the ovary as a cyst, some three, four, six or more centimeters in diameter, usually to recede and disappear after the conclusion of this menstrual cycle. If perhaps half of normal corpora lutea may be considered of sufficient size to be called a cyst, perhaps only one-fourth are of clinical interest. The luteal cells are stretched out over the interior of the cyst, completely losing the festooning arrangement, and becoming only a few cell layers thick. In the usual corpus luteum, as its age progresses in its life cycle of fourteen days, a very constant period of time as a rule, the lutein cells become larger, finely granular, continue to have the yellow color, even with the hematoxylin and eosin stains, and there develops an increasing, delicate, connective tissue around the interior of the corpus luteum, which becomes more compact and fibrotic immediately before menstruation. Also, previous to menstruation, there develop minute blood vessels which ex-

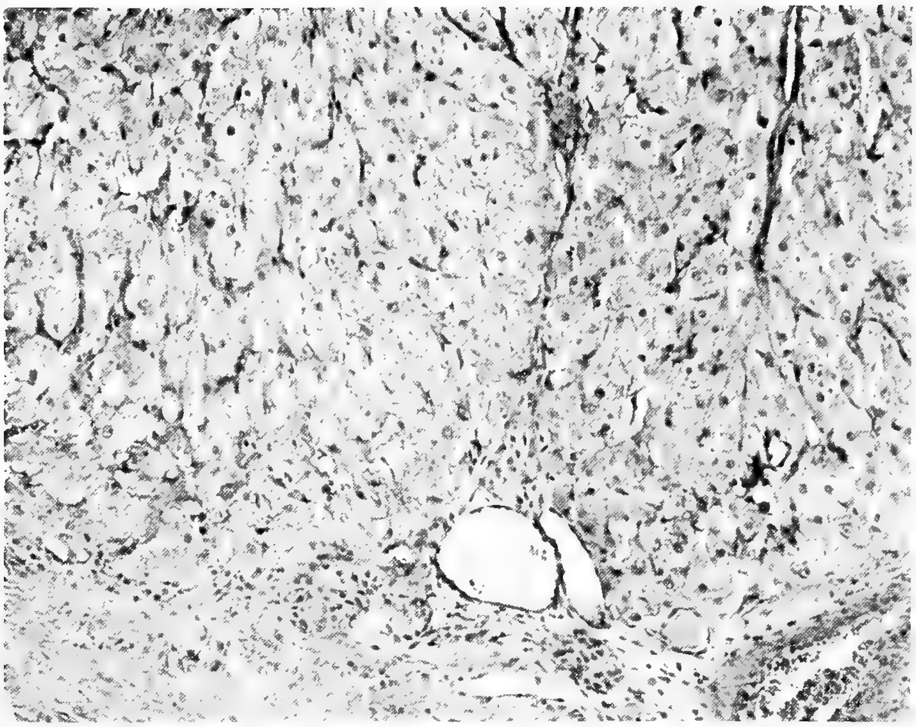


Fig. 218. Corpus luteum of pregnancy.

tend up between the lutein cells toward this connective tissue. As the stimulus for the corpus luteum is removed, that stimulus which comes from the pituitary gland, on about the twenty-sixth day of the cycle, the lutein cells rapidly lose their yellow color, becoming clearer, granular, and slightly shrunken, so that there is an immediate change, and the synthesis of progesterone and estradiol is discontinued. The now inert corpus luteum continues to atrophy rapidly, becoming paler, the cells more vacuolated. A month later, this body appears as a small group of vacuolated cells. In still later months, it becomes a small white scar, which continues to have the festooned outline in miniature, reminiscent of its more illustrious history as an active corpus luteum.

Certain abnormalities of clinical importance are to be considered with the corpus luteum. *Mittleschmerz,* or *ovulation pain,* is concomitant with, and follows, the extrusion of the egg into the abdominal cavity, a pain that is most variable from one individual to another. Perhaps half of all women are unable to determine when ovulation occurs and have no noticeable discomfort. On the other hand, many can determine this occurrence, especially if they are cognizant of when it occurs, although the pain may be very slight. Many can date this time readily. Ovulation pain is now well understood by the laity from the popular publications, which allows it to be more readily recognized. In some women, ovulation pain may appear suddenly for the first time, in incapacitating degree, lasting a few hours or one or two days, being localized in the right or left side. It seems to occur more commonly in the right side. But here again, perhaps the fear of appendicitis draws the patient to the physician for observation. Mittleschmerz of marked degree, usually alternating from one side to the other, or occurring in alternate months in the same side, may continue for several months or years, or may never recur after a single severe episode. The cause of the pain is thought to be related to the extrusion of the blood into the peritoneal cavity, yet this must occur in degree each month. Certainly the amount of blood present from ovulation, as noted when patients have been explored for a diagnosis of possible appendicitis, twisted cyst or ectopic pregnancy, may be so little as to seem negligible. The cause of Mittleschmerz is unknown today. There is no treatment, no method of preventing its recurrence in subsequent months. In this instance, treatment of anxiety is more important than treating the pain. The differential diagnosis between mittelschmerz and acute appendicitis, acute salpingitis, twisted ovarian cyst, ectopic pregnancy, or acute enteritis, may be most difficult. When in the right side, there may be rigidity, rebound tenderness, some elevation of the white cell count, some nausea and vomiting. It may be impossible to distinguish these marked symptoms and finding related to physiologic ovulation from acute diseases requiring immediate surgery. Exploratory operation may be necessary to determine the true diagnosis. The bleeding ruptured follicle does not require oophorectomy or excision of the young corpus luteum. If there is sharp bleeding, a figure-of-eight suture is placed through the ovary. The normal appendix is removed. Often the patient seems to have the impression that her appendix was on the point of bursting, when the cause of symptoms was ovulation. Accurate instruction of the patient is the proper course.

The *corpus luteum cyst,* which becomes more obvious in the week after ovulation and which may become quite prominent in the few days before menstruation, up to five or six, or even eight, centimeters in diameter, may cause a continuous pain in one side of the pelvis. More often, these well-formed cysts cause minor discomfort, as to be ignored entirely by the patient, and may be found incidentally by the physician on routine physical examination. If there is no acute pain to suggest the possibility of torsion, the cyst always is observed through the menstrual cycle, as it commonly regresses. Sometimes two or three months must elapse before an unusually large corpus luteum cyst disappears completely (the largest size must be eight or ten centimeters in diameter. Larger cystic tumors probably never are of luteal origin). In most instances these enlarged ovaries return promptly to normal within the week following menstruation.

Rupture of a corpus luteum cyst may occur spontaneously, but probably more frequently follows sexual intercourse. If the husband vigorously attacks the corpus luteum cyst, which may be caught against the wall of the bony pelvis in the process of sexual relations, the unsuspecting wife may suffer severe pain as the cyst is ruptured. This pain may continue for hours, accompanied by increasing hemorrhage into the peritoneal cavity. The bleeding may cease and the patient gradually recover, the hematoma later being palpable and absorbing slowly. On the other hand, the blood loss may be so severe as to produce shock from intraperitoneal hemorrhage. Exploratory laparotomy may be necessary, with suture of the cyst if possible, or excision of the ovary, if the tear has extended into the hilum. One always prefers re-suture and conservation of the ovary if possible. Blood transfusions are given if the intra-abdominal hemorrhage has been severe. This occasional emergency is fully as important as the ruptured ectopic pregnancy. It is important to realize that a badly torn and ragged ovary may return to normal in two or three months if it can be saved, but one should not make a fetish of conservatism.

Prolongation of the life of the functioning corpus luteum cyst is uncommon, but it does occur. This may cause a missed menstrual period, if the progesterone and estradiol are produced without interruption. There may be associated some irregular scant bleeding or spotting. Pain may appear, but usually to a minor degree. This always suggests to the observer the possibility of an unruptured ectopic pregnancy, or the presence of an intrauterine pregnancy with a corpus luteum cyst. Differentiation of this is difficult, though aided to some degree by pregnancy tests. A

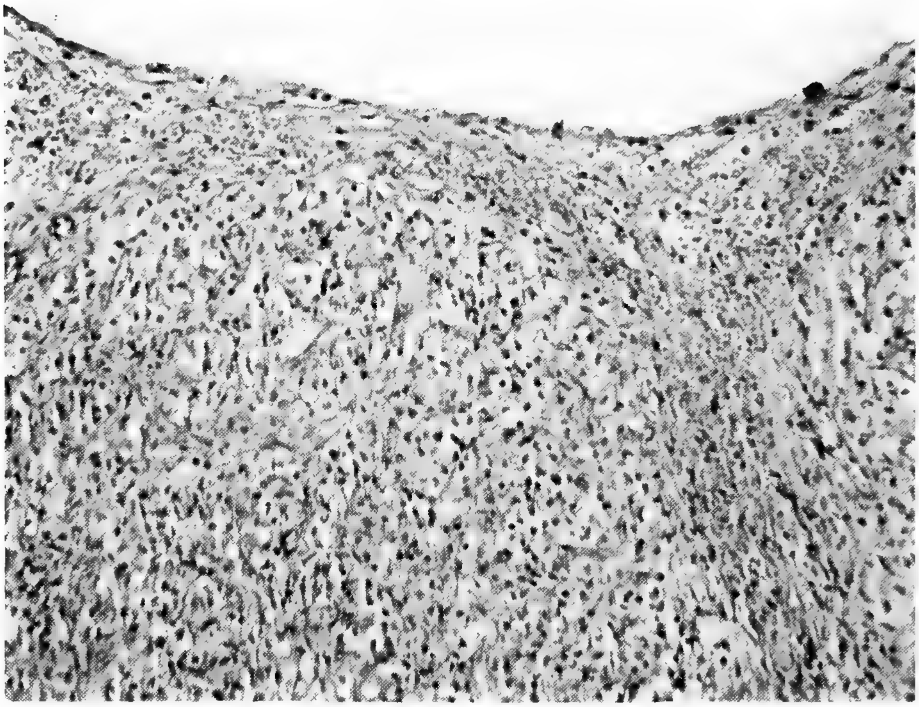


Fig. 219. Corpus luteum cyst. The lutein cells are largely degenerated, granular, shrunken and have pyknotic nuclei. The hormone secretory effect has disappeared. In addition, the inner layer of fibroblastic cells indicates more than two weeks of age.

positive pregnancy test means there is either an intrauterine pregnancy or an extra-uterine pregnancy present, and perhaps only an exploratory operation can determine the exact situation. The use of the culdescope, similar to the cystoscope, which is passed into the cul-de-sac behind the cervix with the patient in the knee-chest position, has been advised by several to make the diagnosis. But, in the opinion of some, the slight risk of perforating a vital structure offsets the value of this instrument. Commonly, careful observation and the passage of time clarify the problem. It is not necessary to operate for a possible unruptured tubal pregnancy, as proper warning to the patient and observation over several days or a week or two are safer procedures than operating, or culdescoping, or needling every patient. Of course, with the unruptured ectopic pregnancy, needling the cul-de-sac would prove fruitless. On the other hand, in certain instances the cul-de-sac needle does aspirate blood which does not clot and indicates intraperitoneal hemorrhage; when there are sufficient symptoms, it may be a valuable procedure. The prolonged functional corpus luteum cyst of woman is similar to the corpus luteum persistens in the cow. The latter corpus luteum is not a cyst; it prevents the cow from having cyclic estrus, and causes sterility. The veterinarian removes this corpus luteum persistens by his gloved hand in the rectum, pinching it away and allowing it to fall free into the abdominal cavity. Most of the delayed or persistent corpus luteum cysts in women eventually absorb. Some do continue for months, cause irregular bleeding or amenorrhea, and may require excision. Apparently, excision breaks the cycle of the stimulus from the pituitary gland, which caused the prolonged life of the corpus luteum cyst.

There is one other form of a short-term persistent corpus luteum, which is responsible for many instances of menorrhagia, or prolonged and profuse menstruation. Such a period of bleeding may continue for eight to

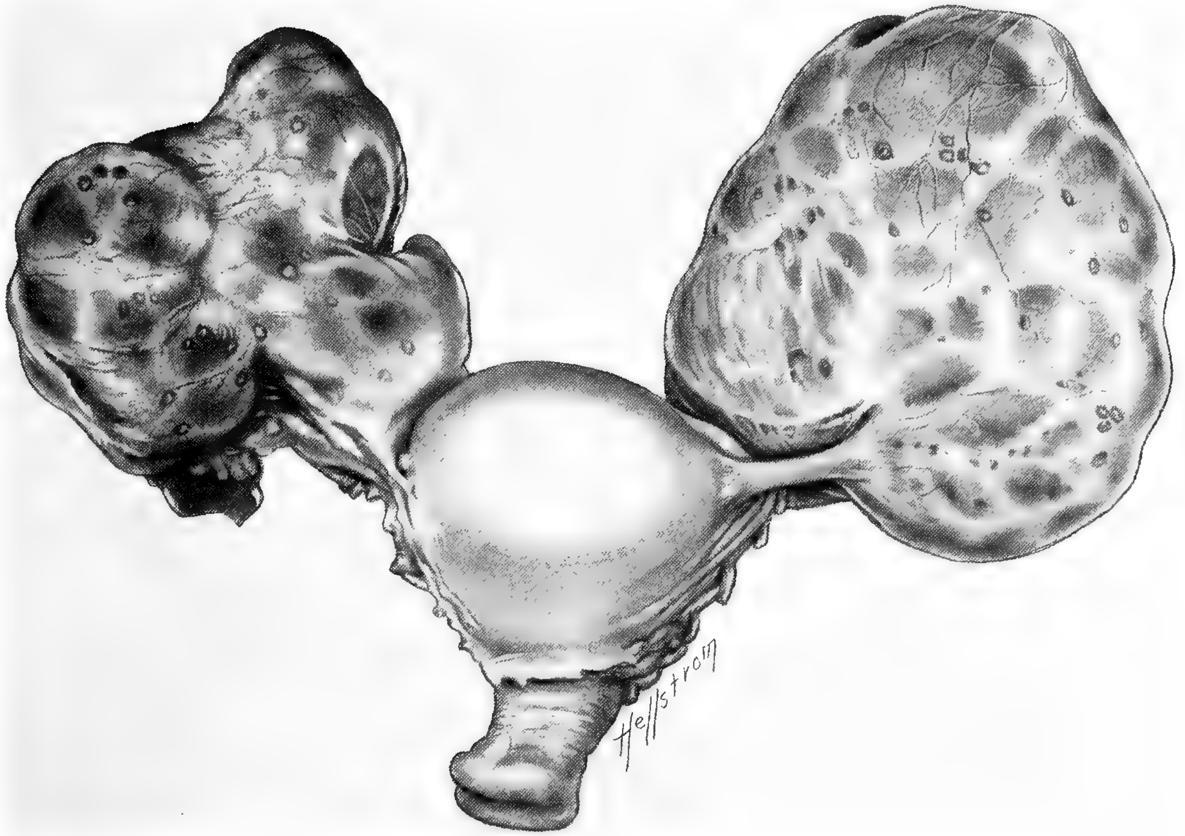
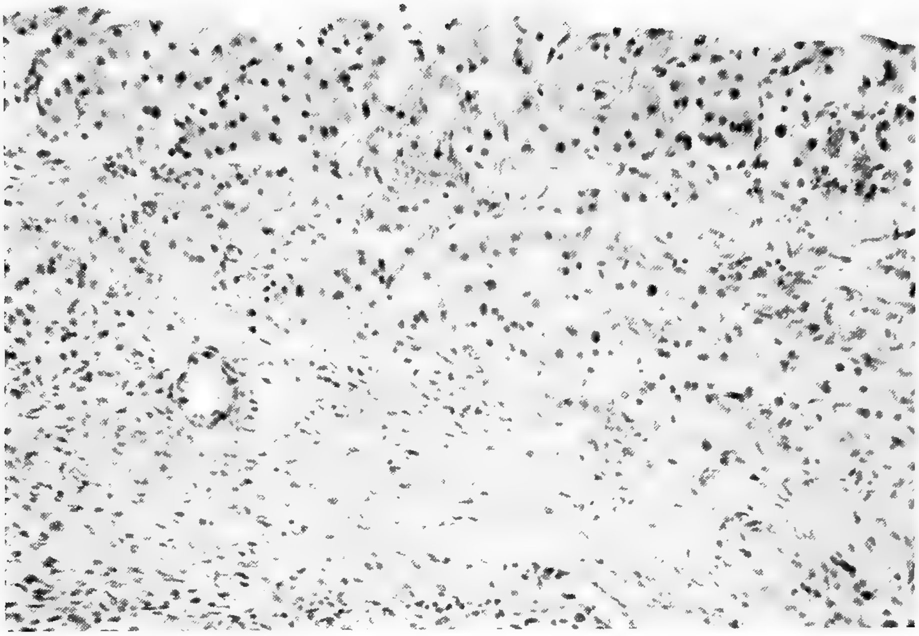


Fig. 220. Lutein cysts of the ovaries associated with hydatidiform mole. A large mole was evacuated from this uterus. After a positive pregnancy test, curettage removed more molar tissue. Repeated pregnancy tests were positive. Small areas of hydatidiform mole were found in the excised uterus. The cystic ovaries would have subsided if all chorionic tissue had been removed. Since the patient was older, had completed her family, and chorioma destruens and chorion-epitheliom were possibilities, excision was performed. Similar cysts may or may not be associated with the latter lesions.

fourteen days, and may be profuse and debilitating. The endometrium, taken at various intervals during this bleeding, continues to show premenstrual or late interval secretory endometrium. There has been a delay in the shedding of the endometrium, so that it has been called "irregular shedding." Apparently, this shedding is delayed because the corpus luteum does not cease its function promptly on the twenty-sixth day, allowing menstruation to occur two or three days later. Apparently some of its function must continue into menstruation, though in much lessened degree, otherwise no fragmentation, necrosis and bleeding would occur. It seems that the stimulus from the pituitary gland, from the LH and LTH, must continue in somewhat lessened degree, but must keep the corpus luteum functioning enough to cause this prolonged menstrual period, though it finally ceases its function and endometrial shedding is completed and bleeding ceases. Menorrha-

Fig. 221. Lutein cyst from case with hydatidiform mole. These are commonly considered theca lutein cysts. Here it appears both the lutein and thecal cells are stimulated by the chorionic gonadotropin. (From case in Fig. 220.)



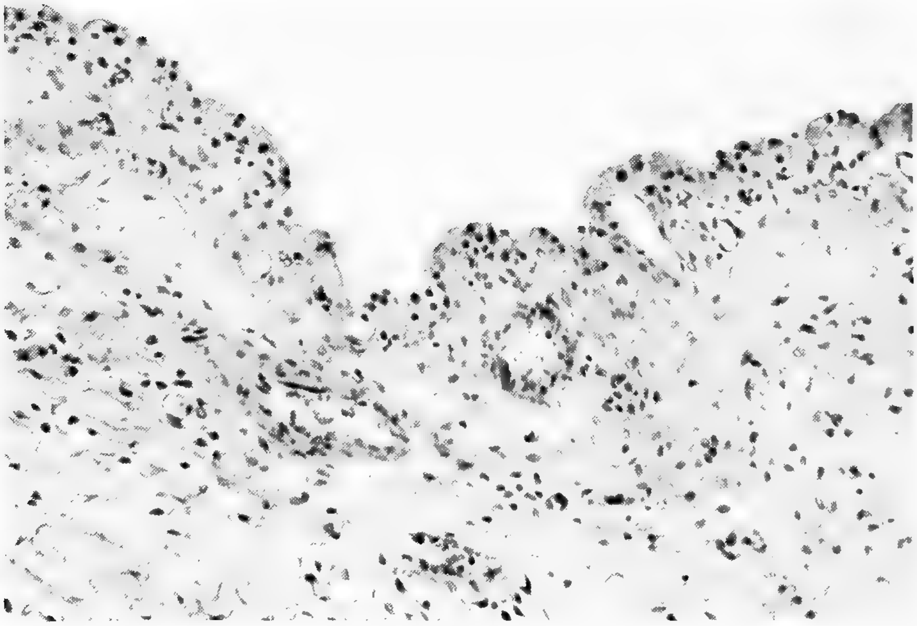


Fig. 222. Lutein cyst from case with hydatidiform mole, showing a thin layer of thecal cells forming the lining. (From case in Fig. 220.)

gia, if functional, is explained in this manner, as a rule. Quite often, menorrhagia seems related to nervous tension, and perhaps this indirectly stimulates the hypothalamus, which may stimulate the pituitary gland, and in turn stimulate the corpus luteum. Some of these patients may be aided by treatment and relief of their anxieties. But in perhaps fifty per cent or more of patients with menorrhagia, there is some organic disease, as a submucous myoma, adenomyosis of the uterus, or chronic salpingitis. It does appear at times that the functional menorrhagia may be helped by curettage. Thyroid extract may be given with improvement of menorrhagia if there are proper clinical indications, which include a sense of tiredness, a lowering of blood pressure, a relatively slow pulse, and a relatively dry skin, corroborated by laboratory tests supporting hypothyroidism.

Theca lutein cysts occur in association with hydatidiform mole and chorionepithelioma. About one-third or one-half of the cases have these cysts of sufficient size to be recognizable. Each ovary may be greatly enlarged, to ten or fifteen centimeters in diameter. The wall of the cysts is lined mainly by thecal cells, the inner lutein cells having largely atrophied. The cysts are characteristically multilocular, thin-walled, and bluish-gray in color. Evidently they are produced by the large amount of chorionic gonadotropin. If all of the mole is removed the cysts disappear. If the cysts persist, some of the trophoblastic tissue must remain. Repeated curettage is indicated if the diagnosis is reasonably clear. If the diagnosis of chorionepithelioma can be established, total excision is indicated.

INFLAMMATORY DISEASES INVOLVING THE OVARY

The second consideration of diseases of the ovary is concerned with inflammations. A primary discussion is given under the previous section on salpingitis, because inflammation of the ovary is essentially secondary to inflammation of the fallopian tube, largely developing from a "boiling over" of the purulent material which drips out of the end of the tube and exudes over the adjacent ovary. The polymorphonuclear leucocytes, serum, and mucous secretion containing bacteria, primarily gonococci, but rarely including streptococci and other pathogens under different circumstances, with their associated toxins and irritants, cause a secondary acute inflammation of the surface of the ovary. This is not a severe inflammation. It does not extend deeply into the ovary, but mainly affects the surface. The exudation of fluids produces a marked "stickiness" of the surface of the ovary and its adjacent structures, which causes them to adhere together. The ovary may be involved in a tubo-ovarian abscess, if the tubal fimbriae become stuck to the side of the ovary, forcing it to become a wall of the abscess. Then the ovary may stretch to accommodate a large collection of purulent material, so that its identity cannot be separated in the abscess wall.

In the later course of tubal inflammation, the pus may be absorbed and may be replaced by serous fluid, so that there remains a tubo-ovarian inflammatory cyst. Apparently, such a cyst may form without being preceded by the fulminating tubo-ovarian abscess, but always it must form from the sealed adhesions of the fimbriae to the surface of the ovary, so that it is the secretion of the tubal epithelium, and perhaps some of the germinal epithelium under the stimulation of irritation, that causes the enlarged cystic structure. The tubo-ovarian abscess and the tubo-ovarian inflammatory cyst are always adherent, and these adhesions, which are usually firm and strong but sometimes of only moderate degree, are the key to clinical diagnosis, particularly if substantiated by a history of pelvic inflammation. On rare occasions, a tubo-ovarian inflammatory cyst is extraordinarily moveable; in this instance preoperative diagnosis easily may be in error.

In the chronic stage of pelvic inflammatory disease, which includes the tubo-ovarian inflammatory cyst, the fallopian tube also may have shrunken to impalpable size, with probably occluded fimbriae or intraluminal occlusions. Nevertheless, the tell-tale evidence is the adherent ovary, which followed the perhaps long-ago boiling over of the inflammation. It usually means the presence of chronic salpingitis, and this may be assumed, provided there are no other diagnostic points that indicate endometriosis. On the other hand, the freely moveable ovary, for practical purposes, rules out chronic inflammation. Pelvic pain, with this finding, must be assumed usually to be of nervous origin.

Abscess of the ovary is rare. On exceptional occasion the ovary may enlarge from inflammation, develop purulent fluid within its interior, and even reach a quite large size, rising into the upper abdomen. It is quite adherent, extremely tender, and may become fluctuant. Usually the associated salpingitis is severe, but on rare occasion the salpingitis may be of only moderate degree and with a free fimbriated end of the tube. This almost suggests that the infection is primary in the ovary in this instance, and yet it is unlikely that the infection did not arrive through the tubal lumen. On occasion, it may be assumed that the bacteria traveled from the cervix or uterus through the lymphatics to the ovary, or that bacteria arrived by way of the blood stream, perhaps arising in the respiratory or gastrointestinal systems. The symptoms and findings of the rare ovarian abscess may seem to be more fulminating, sometimes the abscess seems not to settle into the pelvis, but as a rule the examination is indistinguishable from the usual tubo-ovarian abscess. All pelvic inflammations are treated with various antibiotics, including penicillin, streptomycin, aureomycin, terramycin, tetracylene, and choloramphenicol. The latter may be of particular value because it has been used less frequently, and less resistance may have developed. It is also a broad spectrum antibiotic of great value. When the abscess has become fluctuant, has settled into the pelvis, and can be reached through the vaginal mucosa, the vagina may be incised behind the cervix in the midline and the abscess wall may be perforated with a blunt clamp. The large amount of purulent material may be evacuated. Drains of a T-tube type or Penrose variety are placed into the abscess cavity; these drains are gradually removed from the fifth to the eighth postoperative day, being allowed to remain in place long enough to drain thoroughly the purulent material. When abscesses form that cannot be reached through the vagina, and when they do not respond to antibiotic therapy, laparotomy may be necessary. The abscess may be drained by extra-peritonal incision without invading the peritoneal cavity, using the McBurney muscle-splitting approach on one side or the other. These operations of drainage are generally temporary ones, to allow the patient to recover from the severe acute infection. Usually, later laparotomy is required, with excision of the involved pelvic organs. On other occasions, the abdomen must be opened, and the abscess must be approached boldly, attempting to excise the tube and ovary, or additional pelvic organs. Commonly, this may mean removal of the uterus and both tubes and ovaries. Under these circumstances the operation may be a difficult and formidable procedure. These patients, subacutely ill, have lost much of their resistance, have a rapid pulse rate and low grade fever, and may have serious postoperative complications, including a fatal result. These operations are not to be undertaken lightly. They require careful preoperative study, operative skill and diligent postoperative care.

ENDOMETRIOSIS OF THE OVARY

The third lesion of clinical importance in the diagnosis and treatment of diseases of the ovary involves the rather frequently occurring *endometriosis*. This subject is elaborated upon in detail in another chapter, but because of the diagnostic importance, it is mentioned at this time. Endometrial implants may be scattered throughout the pelvis. They occur in the mucosa or wall of the fallopian tube, on the surface of the ovary and burrowing into its interior to form the retained chocolate cysts, on the surface of the uterus, in the anterior and especially the posterior cul-de-sac, on the uterosacral ligaments and on the bowel wall. When endometrial implants occur, there is extruded menstrual blood in scant amount at the time of menstruation. This blood is quite irritating, causes much discomfort, and is followed by irritation of the adjacent peritoneum, either of the parietal wall of the true pelvis, the fallopian tube, the surface of the uterus or the bowel wall. When the ovary is involved, it becomes firmly adherent to the parietal peritoneum of the wall of the true pelvis. The adherent ovary is a palpable finding of endometriosis. As previously mentioned, it may have its origin in the "boiling-over" of salpingitis. Only when there are additional implants in the depths of the pelvis, which may be palpated in the cul-de-sac as B-B shot nodules, with the forefinger in the vagina and the middle finger in the rectum, can one be reasonably certain that the adherent ovary indicates endometriosis. The uterosacral ligaments may contain the frequently occurring, quite firm, irregular, granular areas, exquisitely tender, which feel like minute cockle-burrs. All of these implants in the depth of the pelvis are extra-ordinarily tender. They are generally felt clearly if present, and they determine with great accuracy the diagnosis of endometriosis, because inflammation producing adhesions is unlikely to be associated with endometriosis, as patent fallopian tubes are the rule with the latter. Of course, a subsequent salpingitis could develop after the endometriosis was well formed.

When the endometrial implants have burrowed into the interior of the ovary, and when this abnormally placed endometrium has bled each month for many months, the retained blood within the spherical space changes to a chocolate fluid. The lining may show only rare portions of endometrium, the remainder being sloughed away. The endometrium which invaded the ovary and formed the cyst also tends to grow back through the cyst wall to perforate, usually on the under or lateral side, and to extrude a small amount of the chocolate material into the peritoneal cavity. This causes the cyst to become even more adherent in these areas, and firmly fixed to the wall of the pelvis. It was for this reason that they were called perforating hemorrhagic cysts of the ovary by Sampson in his first article in 1921. It is the rule that the endometrial cyst is densely adherent. Only on very rare occasions will there be a freely moveable palpable endometrial cyst. This fixation of the cyst along with the telltale implants in the cul-de-sac and on the uterosacral ligaments indicate the diagnosis. The absence of palpable implants or a history of inflammation always will make one doubtful of a diagnosis of endometriosis or inflammatory disease, and raises the possibility of a malignant cyst.

On rare occasion the endometrial cyst may rupture spontaneously, after trauma or even during pregnancy. The spillage of a large amount of chocolate fluid (old menstrual blood) into the abdomen causes the most severe abdominal pain, rigidity, rebound tenderness and degrees of shock. The diagnosis may be difficult before operation, and usually is determined when the abdomen is explored. The involved areas are excised. The ruptured ovary may be resected, leaving normal ovarian tissue if possible. More often the entire ovary must be removed.

TUMORS OF THE OVARY

I. Serous cysts (germinal epithelium)

- Unilocular
- Multilocular

(Parovarian cyst, similar cuboidal or columnar epithelium, but arising from paroophoron remnant of wolffian duct)

- Papillary serous cystadenoma
- Adenofibroma
- Cystadenofibroma
- Papillary serous cystadenocarcinoma

II. Pseudomucinous cyst. (Unknown origin, possibly teratomatous)

- Pseudomucinous cystadenoma
- Pseudomucinous cystadenocarcinoma

III. Primary solid adenocarcinoma (germinal epithelium?)

IV. Secondary or metastatic carcinoma of ovary. (usually serous, occasionally mucinous or medullary)

- Cystadenocarcinoma
- Solid adenocarcinoma
- Krukenberg tumor
- Miscellaneous tumors

V. Dysontogenetic tumors

- Dysgerminoma (undifferentiated sex cell)
- Arrhenoblastoma (male sex wave)
- Granulosal cell tumor (pro-granulosal cell)
  - Thecoma
  - Luteoma
- Gynandroblastoma (mixed male and female)

VI. Other masculinizing tumors

- Masculinovoblastoma (adrenal tumor of ovary)
- Hilus cell tumor (Leydig cell)

VII. Non-hormone secreting tumors of developmental origin

- Brenner tumor (Walthard cell rest)
- Mesonephroma (Wolffian body)
- Dermoid cyst (Twinning)
- Teratoma

VIII. Fibroma (stromal)

- Sarcoma
  - Spindle cell
  - Round cell
  - Fibrosarcoma

IX. Lymphosarcoma

TUMORS OF THE OVARY, BENIGN AND MALIGNANT

The fourth section to be elaborated upon among diseases of the ovary includes tumors of the ovary, both benign and malignant. In the first discussion of ovarian abnormalities some detail was given to a description of graffian follicle cysts and corpus luteum cysts, which cause enlargement of the ovary. These are known as the functional cysts of the ovary, always to be distinguished from the true neoplastic cysts. The functional cysts are usually diagnosed by their presence according to the time of the menstrual cycle, or according to the symptoms of missed menstruation or metrorrhagia. Always one may be mistaken in the interpretation of these cysts, so that they positively must be kept under observation. Any sizeable cyst, and this means a cyst seven or eight centimeters in diameter or larger, that persists longer than six weeks, should be considered as a possible new growth. Exploratory laparotomy usually is indicated. In some instances one may decide to delay surgery for longer periods of time, but great care must be exercised in determining this point, especially in the older woman.

The *serous cyst* is a rather frequently occurring cyst of the ovary. It develops from the germinal or surface epithelium of the ovary, which apparently has been trapped in small areas in the depth of the convolutions of the ovary. While minute cystic structures are quite frequently found in normal ovaries, it is only under some unknown circumstances that one of these minute cysts enlarges to form an

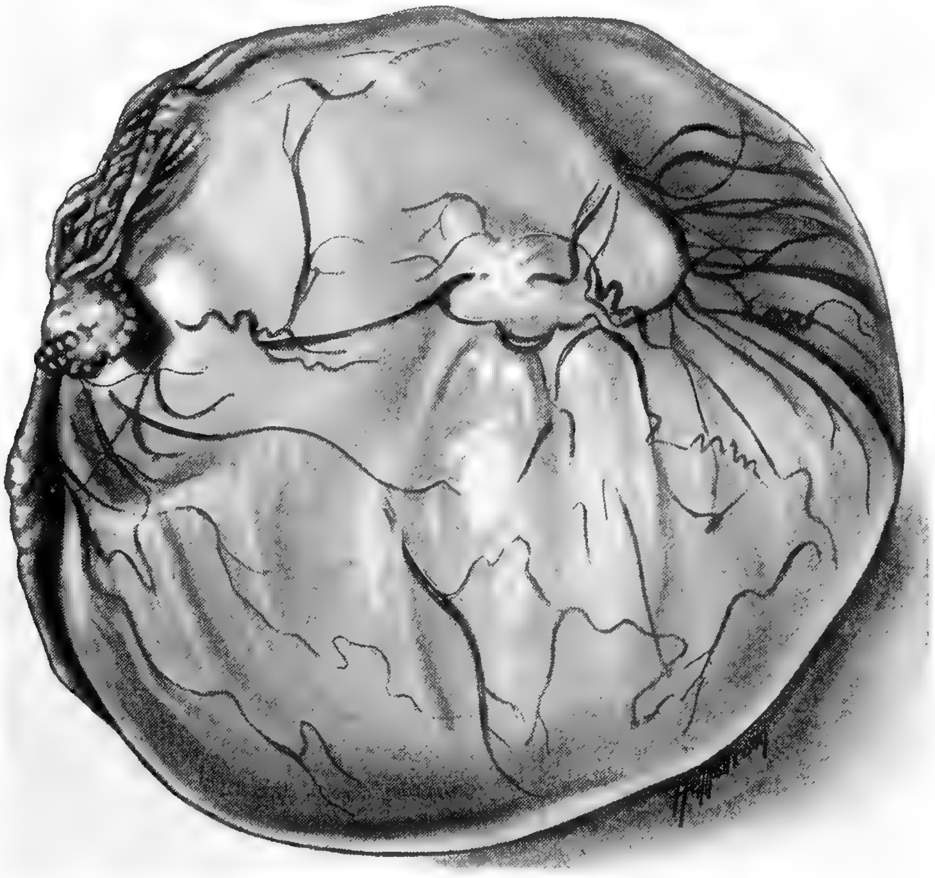


Fig. 223. Multilocular serous cyst. Thin walled, with compartments, lined with single layer of cuboidal cells (germinal epithelium). Benign. The small blood vessels are prominent on the gray background.

ovarian cyst of clinical importance. Such a cyst may gradually enlarge to great size, and may contain many liters of clear, watery fluid. The lining is composed of a single layer of cuboidal epithelial cells, darkly staining, with regular, somewhat vesicular nuclei. Not infrequently there are septa across these cysts, which perhaps means that more than one of the minute cystic structures enlarged simultaneously to form the cystic mass. At any rate, such septa and divisions within the cyst are frequent. This is then called a multilocular serous cyst. This serous cyst, whether unilocular or multilocular, may be unilateral or bilateral, and is strictly benign, unless there develops papillary forms, to be described presently. The large serous cysts often have been tapped by paracentesis, removing generous amounts of fluid. The cyst usually becomes adherent to the abdominal wall after recurrent tappings over prolonged periods of time. The diagnosis, when repeated paracentesis is done, usually is not made, and the patient is considered to have ascites of cardiac, liver or unknown origin. Before proceeding further, a mention of the *parovarian cyst* seems in order. This again is a serous cyst, arising from the paroophoron, a remnant of the wolffian duct system in the broad ligament. This cyst is not uncommon, and when relatively small, of six to eight centimeters in diameter, seems to be adherent, the mobility being limited by the leaves of the broad ligament. This seeming adherence may confuse the diagnosis with tubo-ovarian inflammatory cyst. The parovarian cyst is mentioned now because it is a serous cyst, quite thin-walled, lined by a single layer of low cuboidal epithelium, always benign, never producing papillary forms as with the serous cyst of the ovary. It may seem at surgical exploration that one is dealing with a serous cyst of the ovary. Only when the small atrophic or normal ovary is found attached near one side of the cyst is the true nature clear. This cyst behaves in a manner similar to the serous cyst, except that it is always unilocular and benign. It may reach a tremendous size, and again has been tapped frequently by paracentesis, removing a very clear watery fluid, which in older times was described as "spring water." This slightly bluish appearance of looking into a deep spring was noted from the appearance of fluid collected in white earthenware or stone crocks. The paroophoron extends in the broad ligament parallel to the fallopian tube and down alongside the uterus and vagina, where it is named the Gartner's duct. Cysts may develop at any point in this duct, but are more frequent in the broad ligament and in the side walls of the vagina. The cysts in the vagina have been mentioned in the section of diseases of the vagina. From the end of the fallopian tube there may occur small cystic structures on quite elongated stalks, called *cysts of Morgagni.* These are so frequent as to be normal, especially those less than one centimeter in diameter. On extremely rare occasion the cyst of Morgagni may enlarge to six or eight centimeters in diameter. They may develop a twisted pedicle, and become gangrenous. Again they are lined by a single layer of flattened serous epithelial cells and are never malignant.

The *papillary serous cystadenoma* is a serous cyst, which has a papillary growth on its interior or on its exterior, or both. It is commonly multilocular. In fact, multilocules are the rule. The tumor is bilateral in more than fifty per cent of the cases. The cyst is always fluctuant. It contains a clear fluid which is rich in serum proteins, including serum albumin and globulin. Sometimes, the fluid becomes dark, of chocolate appearance, due to old blood within the cyst from hemorrhage, related to pressure or injury or even slight torsion. The papillomatous growth on the interior of the cyst, or on the exterior, has a surface of cuboidal or low columnar cells, rather dark with homogeneous nuclei in a single layer. The cells may resemble tubal epithelium with ciliated and secretory forms. This single layer is stressed because it means a benign tumor. Actually, there may be

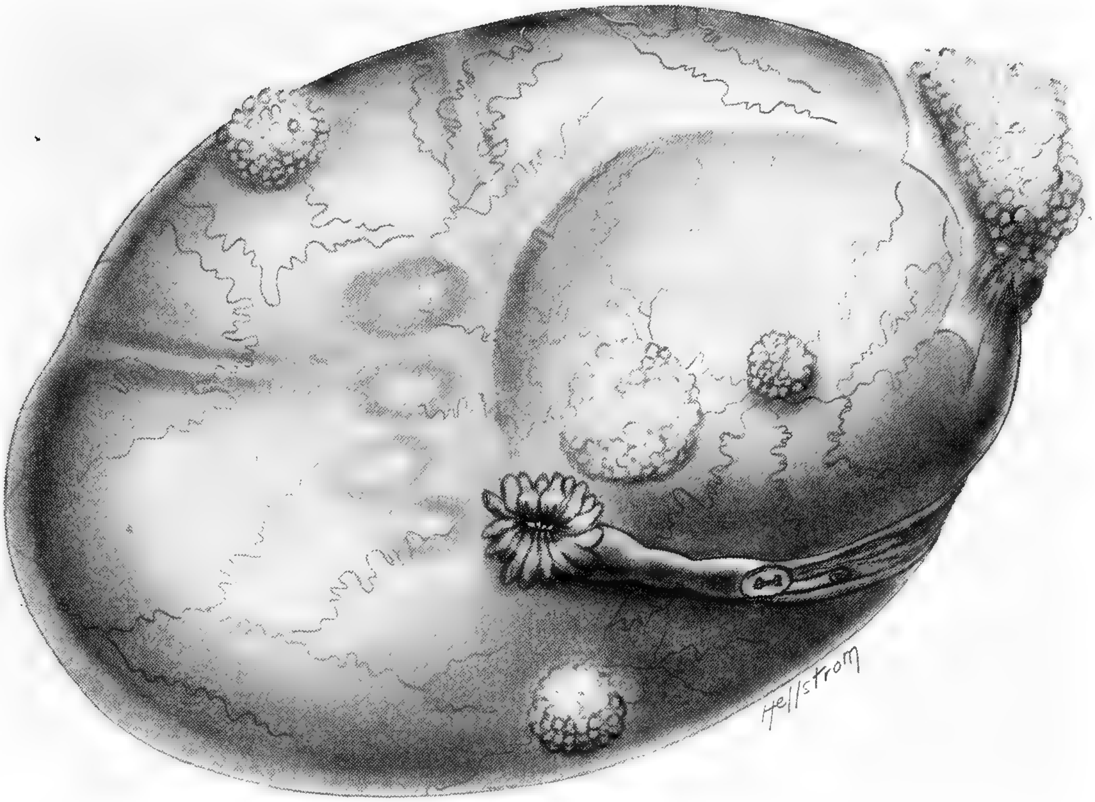


Fig. 224. Papillary cystadenocarcinoma. Multilocular cyst with papillary tumor in interior and extending through the capsule. Grossly this could represent papillary cystadenoma or papillary cystadenocarcinoma. Here the cells were piled up several layers thick and showed abnormal changes.

slight piling up of two or three cells at times, but the nuclei, though staining darkly, are regular, and such tumors continue to be benign. Frequently microscopic sections show areas of the tumor with several cells thick, and this may be caused by tangential section across the single layer of cells in the same plane. The papilloma, or warty growth, which extends through the capsule of the cystic tumor, may extend onto the parietal peritoneum in the depth of the pelvis or the peritoneum over the surface of the uterus and bladder and over the fallopian tubes. Often this extension remains of slight or moderate degree in the depth of the pelvis. But such papillomatous growths may extend over the entire abdomen, seeming to cover every portion of the parietal and visceral peritoneum. These papillomatus growths always secrete serous fluid into the abdominal cavity and may cause a severe degree of ascites. For many years, it has been taught that if the primary tumors are removed, the extensions of these benign papillomas may regress. There is little on record in the literature to support this contention, but it remains a hope in every case. Removal of the primary tumors is always indicated, if possible. In some cases with extensive benign papillary growths, the fluid is secreted in the abdomen over a period of many years, requiring numerous paracenteses to remove this fluid which may re-occur every few weeks. If sufficient time elapses, and this may be one year or a number of years, the benign papillomatous growth tends to change to carcinoma. It becomes a papillary cystadenocarcinoma in the ovary, and papillary adenocarcinoma in the implant.

Sometimes this tumor, unilateral or bilateral, forms only small cystic enlargements of the ovary, but a profuse papillary growth over the surface. These ovaries may be only slightly enlarged, but on cut section in the interior do show small papillary cystadenomas. This so-called "warty ovary" may become large, forming firm papillary tumors filling the true pelvis. As a rule when the growth has reached some size, there is extension of the papillomas onto the local or general peritoneal surfaces. This papillary growth may remain microscopically benign, and not invade or metastasize for a long time. However, they do cause increasing debility, probably from the secretion of fluid containing blood proteins, and such tumors probably always become malignant, in varying degrees of time. It is impossible to determine whether the papillary cystadenoma of the well-formed cystic type and the solid form of papilloma or warty ovary are benign or malignant by gross appearance. Only by microscopic studies can one determine if the papilloma is a non-metastasizing, though locally spreading tumor. It is to be carefully pointed out that these tumors change to carcinoma in patches or small areas, which change gradually extends through the entire tumor, so that a sample block taken from one area may be benign, but in some other area the tumor may have changed already to a malignant growth. Thus, caution is always necessary, when the sections from only a few blocks are benign, because one more block may show carcinoma.

The papillary cystadenoma of the ovary at times is diagnosed, or suspected, after x-ray studies have been made for other reasons. The film of the abdomen may show a precipitation of calcium granules in the pelvic area, which may be due to minute calcifications in the papillae of the cystadenoma or cystadenocarcinoma. These small areas of calcifications, usually occurring in the papillomatous projections, are quite common in these tumors.

It has long been considered that at least fifty per cent of the papillary cystadenomas become malignant. More likely one hundred per cent become malignant if they remain present long enough. It is also true that fifty per cent of the tumors when seen are already malignant. As one finds the papillary cystadenoma-type of tumor in the pelvis there is a fifty-fifty chance that it will show true malignant changes microscopically.

The treatment is surgical. Because of the malignant potentialities of these tumors, the best treatment is bilateral salpingo-oophorectomy, with total hysterectomy. There are extenuating circumstances, and one will wish to be as conservative as possible within reason. In young women, and especially the young woman highly desirous of having children, one would think carefully before removing a normal appearing and apparently uninvolved ovary, when the other ovary contained a tumor. If it could be determined clearly and definitely that the growth was benign, certainly excision of only the involved ovary is indicated. As stated above, even with careful pathological studies with multiple blocks, a small area of carcinoma may be missed. The random sample, especially that taken for a frozen section, may be quite inaccurate for a definite opinion.

In the case of the quite young person one would be inclined to remove only the involved ovary, if it seemed probable to represent a benign papillary cystadenoma. If, after careful pathological examination of multiple blocks taken after the operation, there was found definite carcinoma, the best treatment is reoperation and removal of the remaining ovary and uterus, though grossly normal. This is because of the fifty per cent possibility of recurrence in the other ovary. Perhaps this estimate is too high or too low, but certainly the possibility of recurrence in the other ovary is strong, and unless the patient chooses to take the risk, then re-operation is the better treatment.

If there are papillary implants on the pelvic peritoneum, and localized to this area, one would choose to remove that peritoneum if possible, or one might use electro-dessication or fulguration in the local areas, taking care not to harm the major vessels and ureters beneath the peritoneal surface. On some occasions surgeons have placed large cigarette drains down to the area of the papillomas, hoping that some secondary infection, which always follows, might destroy papillary implants. More often one would hope that removing the primary tumor would be followed by disappearance of the implants. Certainly if there was any suggestion of malignancy with local implants, the surgery is followed by intensive deep x-ray therapy. There is interest in instilling radioactive gold in the peritoneal cavity at the time of surgery or shortly thereafter, through polyvinyl tubes. Also local chemotherapy is being used, with some skepticism of the results, at present.

The *adenofibroma* of the ovary is related to the papillary serous cystadenoma, and minute ones are frequent findings in the examination of otherwise normal appearing ovaries. They may appear as small raised nodules on the surface of the ovary, are much more fibrous, with more intercellular collagen, and are covered over with a single layer of germinal epithelium, the low cuboidal epithelium that is normally present over the surface of the ovary. These small nodules may become much enlarged to form firm fibrous tumors several centimeters or more in diameter and have gross papillary projections from the surface. This is the typical form of the quite benign adenofibroma of the ovary. The *cystadenofibroma* of the ovary is a similar tumor, with some cystic spaces within it, lined by the single layer of the germinal epithelial cells. These cysts are not prominent in the adenofibroma as a rule. While it is quite conceivable that this tumor may become malignant, forming a sarcoma from the stroma, this must be very rare. The other possible change would be the development of a papillary adenocarcinoma, which though rare is more frequent than sarcoma.

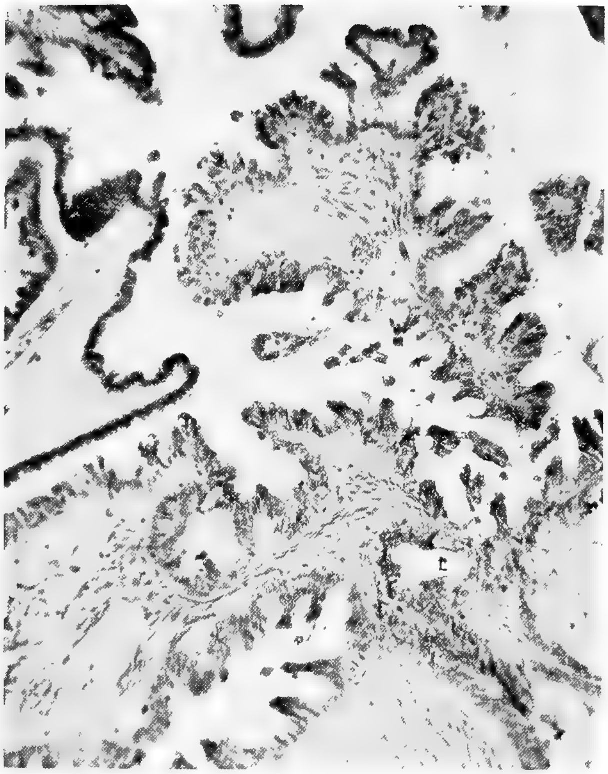


Fig. 225. Papillary serous cystadenoma of the ovary. The papillae of this tumor are covered over by one or two layers of ragged, serous epithelial cells. The nuclei are essentially regular although some do show mitoses. The slight piling up of cells in areas is suspicious of early malignant change.

The *papillary serous cystadenocarcinoma* always may arise from the papillary serous cystadenoma, though no one knows this is invariably true. Perhaps the tumor may have its inception as a malignant growth without a precedent of benign papillary serous cystadenoma. At any rate, these tumors are akin in appearance to the papillary serous cystadenoma, and, as stated above, may be very difficult or impossible to distinguish from the benign tumor. This tumor again is bilateral in at least fifty per cent of the cases and is usually multilocular. The cyst has a rather thick white capsule and is fluctuant, though sometimes so tense as to seem solid on pelvic examination. The cysts may be of relatively small size, but usually when discovered, are ten or twelve centimeters in diameter. They may reach a quite large size, larger than a term pregnancy. Frequently, by the time the tumor is discovered, there is extension from around the cystic tumor to the peritoneum and adjacent organs. The papillary growths on the surface of the tumor have a firmer appearance, congeal themselves together in nodules of granular tumor, and, as mentioned, extend from the surface of the cyst along the mesovarium or on to adjacent surfaces of the bowel wall, uterus, and parietal peritoneum. Papillary implants appear throughout the abdominal cavity, if the tumor has been present long enough. Sometimes, these implants have not extended above the pelvic brim; at other times, they have not extended beyond the ovary, which of course gives a better chance of cure for the patient. The gross appearance of the yellowish and granular papillary carcinoma, with firm nodules growing into the omentum, mesentery, and bowel wall, usually is distinguishable from the benign papilloma, which is entirely on the surface, softer and more warty appearing. Enlarged lymph nodes may be felt in the pelvis or along the aorta. Palpation of the liver may reveal metastatic nodules. The well-formed carcinoma usually is readily distinguished, especially when it has extended through the abdominal cavity.

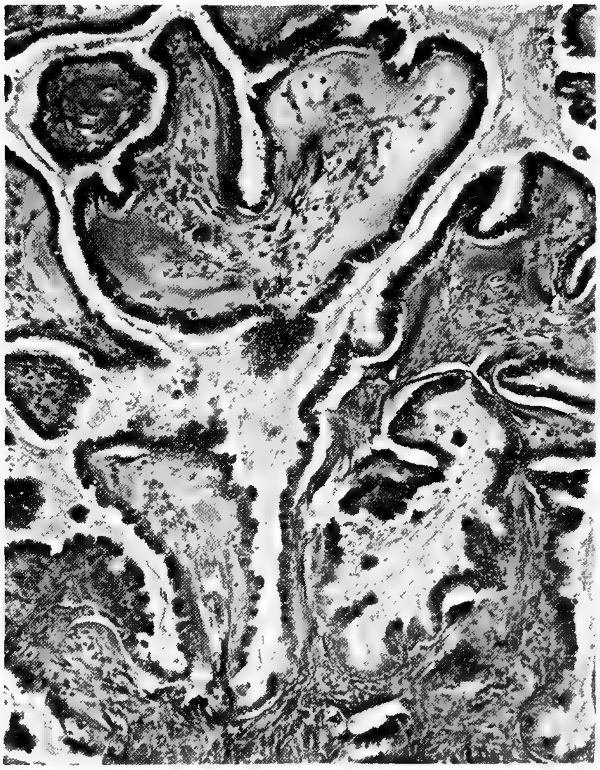


Fig. 226. Papillary cystadenocarcinoma of ovary. Note piling up of cells.

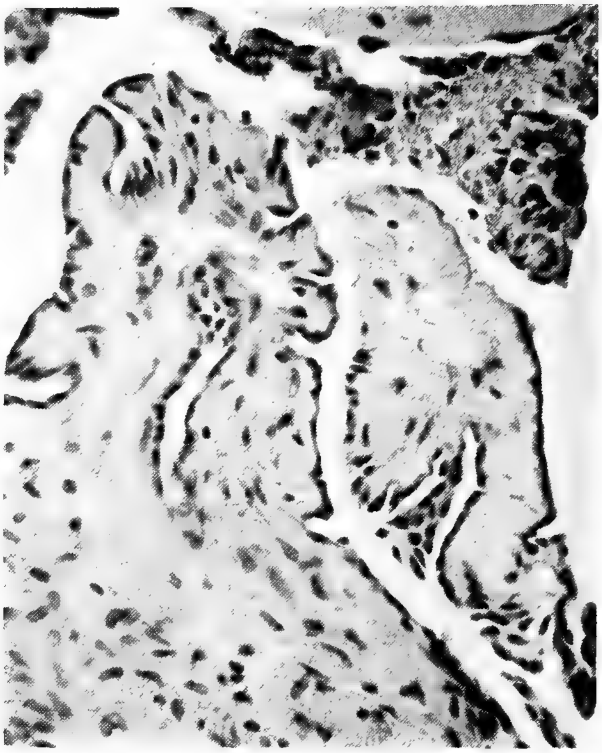


Fig. 227. The papillary adenofibroma of the ovary. A benign lesion with marked fibrous tissue stroma covered over by a single layer of germinal epithelial cells. In the upper right central portion the masses of cells apparently have been cut tangentially from other papillae. This is considered a benign lesion, but is pre-malignant.

Microscopic examination reveals the papillary arrangements of delicate stroma of fibrous tissues are covered by epithelial cells which are changed from small regular cuboidal cells in a single layer to larger, paler cells, variable in size and shape, and always piled up in several layers. The irregularity of the nuclei, the pyknosis, the mitoses, both as normal forms

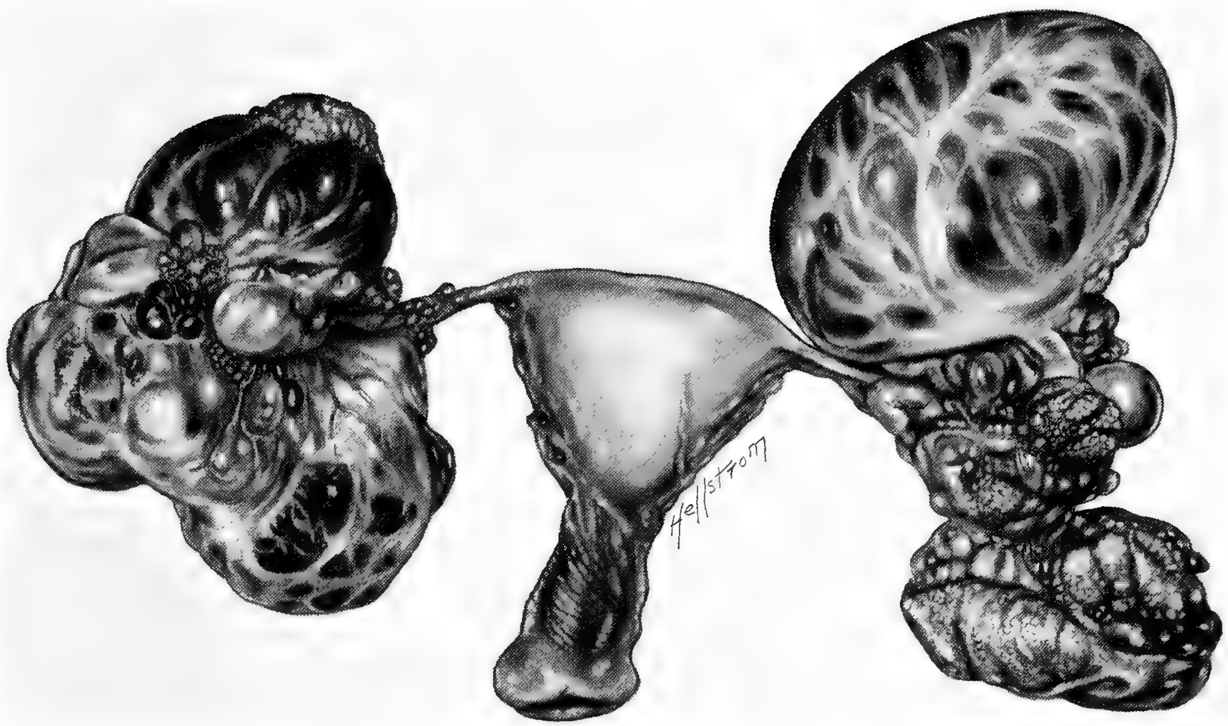


Fig. 228. Papillary cystadenocarcinoma of both ovaries, adherent, with implants on pelvic peritoneum. Operation followed by intensive x-ray therapy. Patient died two years later with metastases in lungs. More frequently the recurrence is in the peritoneum.

and especially as abnormal forms, make it clear that this represents a malignant growth. The tumor cells are seen to invade the cyst wall itself, and extend on to the surface of the cyst. The extensions and the metastases to the peritoneal cavity have a similar appearance.

The age of appearance of this largest group of cystadenocarcinomas is any age, because the tumors are found in infancy and adolescence, though rarely, and may be found throughout menstrual life, more near the age of forty to forty-five years, but actually they occur most frequently postmenopausally. The symptoms are none; that is, the symptoms are none when the tumor is developing, when it has not extended beyond the capsule, when it does not become so large that it presses on other organs or causes a protuberance of the abdomen, which the patient herself notices. There is no pain with this growth, until the tumor has extended beyond probable cure. Certainly pain and abdominal distress, when present at the time the tumor is discovered, are most serious symptoms. To be curable in appreciable degree these tumors must be diagnosed before they have extended and have caused symptoms. This means that the patient must be seen and examined at regular intervals, at least every six months, with a thorough and careful bimanual pelvic examination. At each pelvic examination, all of the pelvic organs are carefully surveyed, and a Papanicolaou cytology examination is performed at least once yearly. With a vigorous campaign to detect ovarian carcinoma before it has spread, many harmless benign cysts of the ovaries will be removed after the menopause, and exploratory operations will be performed, which seem unnecessary in retrospect. If one is not over-balanced in a zeal for surgery, then these negative surgical operations are not to be condemned, but to be well recognized as a standard degree of error.

Any ovarian tumor or cyst larger then nine or ten centimeters in diameter, or larger than a large orange, which is present for six weeks or longer, should have exploration and excision, because of the possibility of carcinoma of the ovary. At times, these tumors will prove to be pedunculated fibroids of the uterus, benign serous or dermoid cysts, or small tubo-ovarian inflammatory cysts. In many instances, the surgery might have been unnecessary, if one could have known that the nature of the tumor was benign. Every effort must be made to make a thorough and accurate diagnosis. At the time of surgery, if the impression is carcinoma of the ovary, as a rule both tubes and ovaries and the entire uterus should be exercised. This is indicated, even though there is extension of the tumor onto the local pelvic tissues. If there is extension throughout the abdomen, or if there are areas of metastases, removal of the primary lesions should be performed, provided the pelvic tumor can be excised without extra-ordinary hazard. The patient is already under such extra-ordinary hazard that almost no surgical risk could exceed the predicament which is present. Primary surgical excision, if there are no apparent implants or extension, will cure a reasonable percentage of patients, perhaps sixty per cent. If there are implants and extensions in the depth of the pelvis, perhaps thirty per cent may be cured after excision of pelvic organs and intensive irradiation therapy, preferably by high-voltage or cobalt therapy. If there is extension throughout the abdomen, the cure is probably zero, although one hears of the rare case apparently relieved by generalized abdominal x-ray therapy, after excision of the primary tumors. As a rule, excision of the primary tumors gives the patient her best hope for improvement. It has long been felt that, in occasional cases with extension

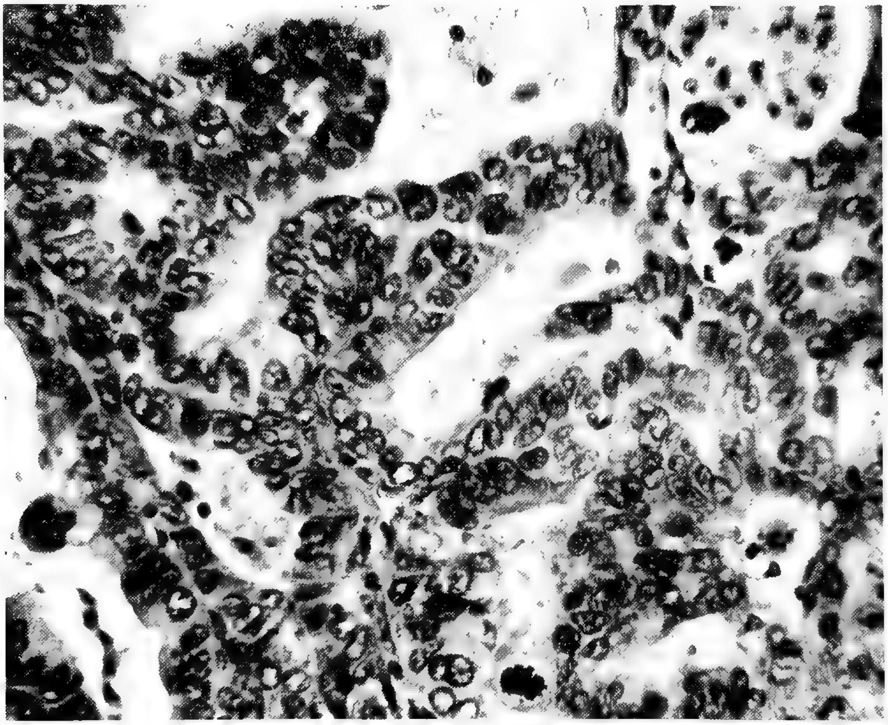


Fig. 229. A papillary adenocarcinoma of the ovary. The glands are largely back to back and covered with two or three layers of cells. There is marked irregularity of nuclei. Note the large giant nucleus in the left side of the photograph. Two years after excision and x-ray therapy, the patient died from metastases in the lungs. (From case in Fig. 228.)

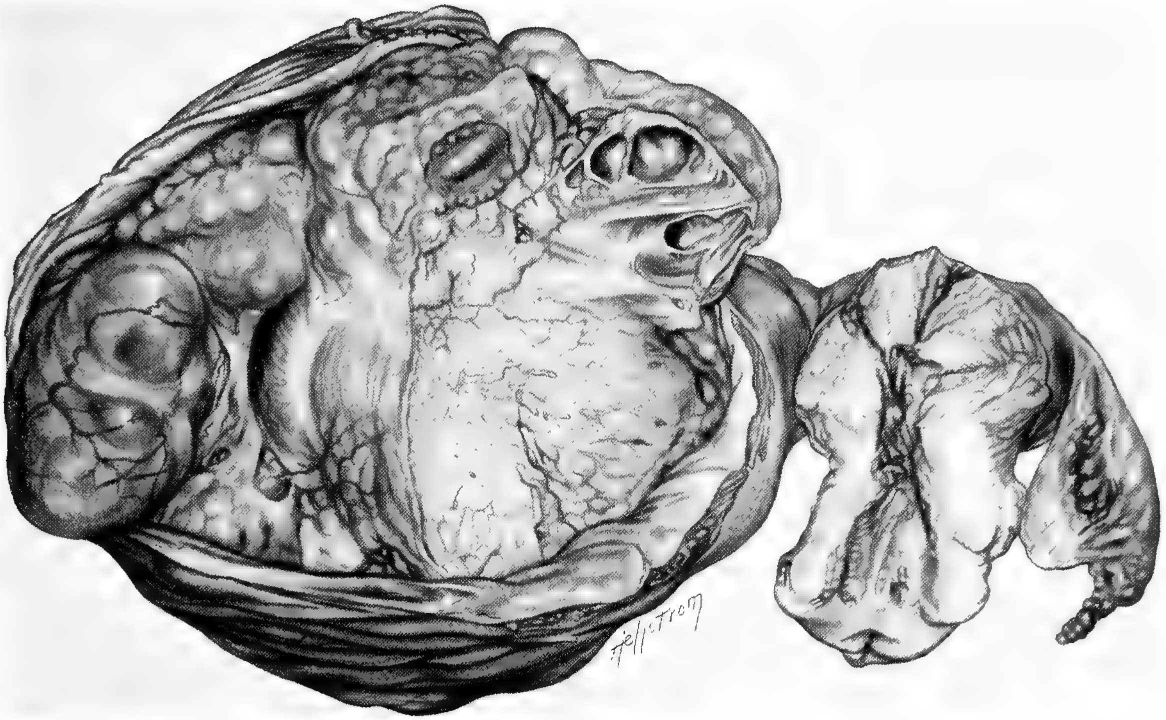


Fig. 230. Cystadenocarcinoma of left ovary, age sixty-five years. Much of the tumor is solid adenocarcinoma, of yellowish, granular appearance. Endometrium shows hyperplasia pattern. Source of estrogen undetermined. No implants or distention. Cured by excision only.

and metastasis, excision of the primary tumors may be followed by regression of the tumor and apparent cure of the patient. While this must be an exceedingly rare occurrence, it does appear to be true. One may assume there is some hormone relationship to the mother tumor. After the wound of the surgical operation has healed, or about ten or twelve days after operation, deep x-ray therapy is started. This is continued until the tumor dose, of three to five thousand r is delivered to the depth of the pelvis or to the areas in the abdomen in which the tumor seems to be congregated. Radiation therapy may be given by the x-ray machine of 200 KV or 400 KV. It does seem true that the 1,000,000 and 2,000,000 volt x-ray machines, the high voltage cobalt machines (2,500,000 volts), and the betatron with 25,000,000 volts, may deliver larger doses of irradiation therapy (up to 6,000 r tumor dose) more quickly and with less reaction to the skin and abdominal wall. It is not precisely clear as to how much irradiation the abdominal contents can take, but it does seem that the larger doses given by the larger machines, while destroying more cancer, also cause profound changes in the vital organs, including the small and large intestines. The bowel becomes severely thickened, functions poorly, and often there is prolonged diarrhea for many years, with associated debility. Not only do the walls of the intestine become thickened, but also the parietal peritoneum, bladder, greater blood vessels, muscles and bones are affected. Extremely dense abdominal adhesions are formed, and irradiation invalidism may follow. This means all is not simple in the use

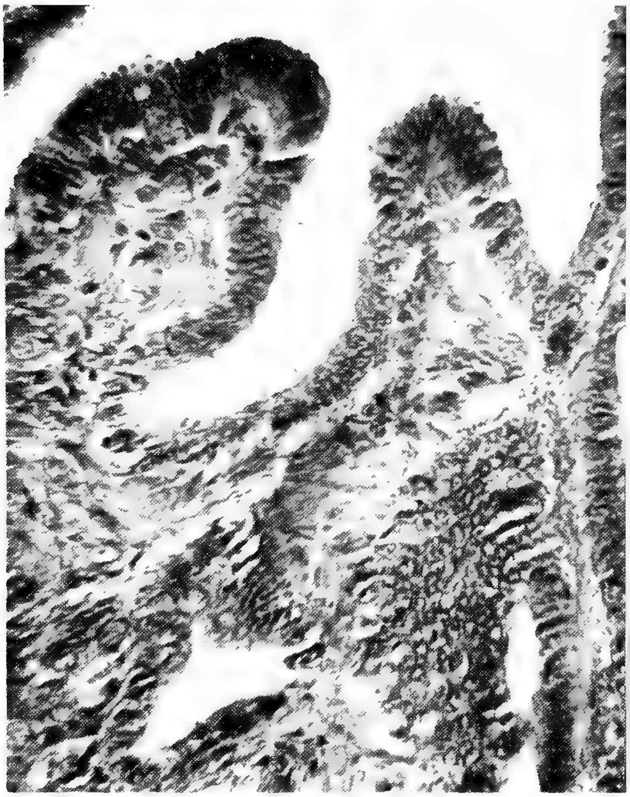


Fig. 231. Papillary serous cystadenocarcinoma of the ovary. The large papillae extending into the cyst are covered over with a multi-layer of serous epithelial cells. The nuclei vary in size and shape and there are increased mitoses. (From case in Fig. 230.)

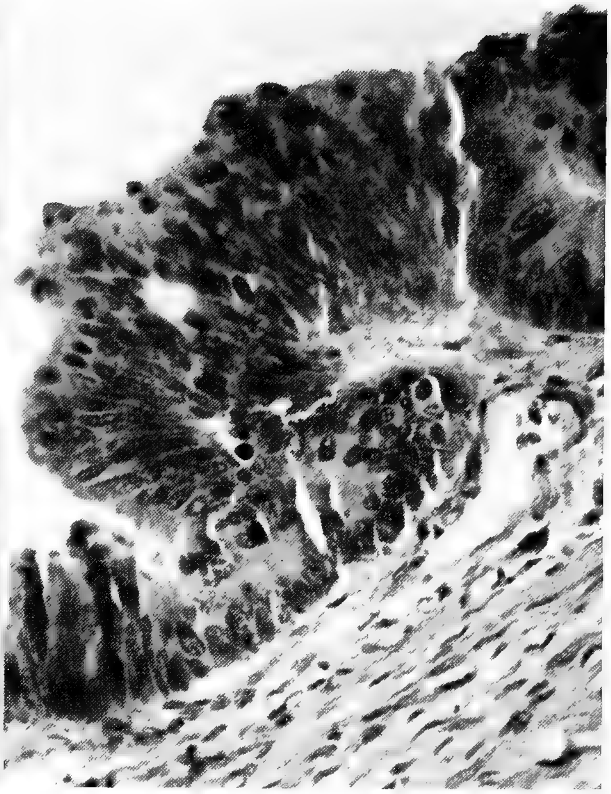


Fig. 232. Papillary serous cystadenocarcinoma of the ovary. A high power view showing marked growth of the serous epithelial cells piled up many layers thick. The nuclear changes are obvious and there are increased mitoses. (From case in Fig. 230.)

of irradiation therapy. At times, treatment must be discontinued because of diarrhea, or severe nausea and vomiting, so that the application of the irradiation therapy may be difficult. Some have suggested leaving the uterus in place, after removing the primary tumors, in order that a large dose or radium may be administered into the uterus, attempting to affect the tumor that may be adjacent to the uterus. Since the effect of the radium is rapidly dissipated from each increasing centimeter distance from its source, one is inclined to believe that leaving the uterus intact for this purpose adds little. Certainly one is not treating the uterus itself, because metastasis and recurrence here is minimal or infrequent. Perhaps one might say that there is no need to remove the uterus, and this may be true. But since extension is thought to occur from one ovary to the other, spreading down the lymphatics around the fallopian tube and across the fundus of the uterus, it seems logical to remove the pelvic organs in toto when dealing with ovarian cancer. Under some circumstances, the abdomen may be explored and extensive tumor may be found, which cannot be excised. After biopsy, deep x-ray is given. Occasionally, shrinkage of the pelvic tumor follows, re-operation may be performed, and the primary tumor possibly may be removed. This has been mentioned at intervals in the literature. At the time of excision of the pelvic organs, when there is evidence of extension and metastasis in the abdomen, some have advised that small polyethylene tubes be left in the abdominal cavity, leading out the incision, through which there may be instilled radio-active gold solution, twenty-four to forty-eight hours later. The gold apparently is attracted more to the malignant cells, and carries with it the lethal effect of the irradiation present from the radio-active atoms. Others have placed the radio-active gold directly in the abdomen at the time of operation, but usually this material is not immediately available, as it has a short life and must be obtained on special order through the Atomic Energy Commission. After operation, when the microscopic diagnosis is conclusive, and especially with the recurrence of ascites, one may drain away the fluid with a trocar and instill radio-active gold solution at any time. The value of this application is praised by some and questioned by others. Some have reported improvement in varying percentage of cases, but no cure of any well formed cancer. Several authors have claimed that ascites has been abated by the radio-active gold; others have discounted this improvement to any major degree; and many remain skeptical as to any real value from this treatment.

Chemotherapy has offered some extraordinary and interesting ideas in recent years. There are a number of different compounds that may be used in the treatment of malignant tumors. Nitrogen mustard has been given intravenously and intraperitoneally, with apparently some degree of improvement. Triethylene phosphoramide (TEPA) and triethylene thiophosphoramide (THIO-TEPA or TSPA) have offered exciting hope as a great advance in the treatment of carcinoma of the ovary. These chemicals seem to have a more destructive effect on ovarian cancer than other cancers, and some authors have reported remarkable regression of tumor over a period of months. Thio-tepa may be given in ten milligram doses intramuscularly every other day for five days, after which none is given for at least three weeks, to determine the effect on the bone marrow as reflected in the blood count. This drug is extremely toxic to the bone marrow and may cause severe anemia and agranulocytosis. When reactions are severe, the drug must be discontinued. Slowly the bone marrow may recover. In the author's experience the effects of TSPA have been disappointing, but these new chemicals may point the way to an eventual cure of carcinoma. Because papillary serous cystadenocarcinoma is the most frequently occurring malignant tumor of the ovary, more attention has been given to complete treatment in this section. These principles largely are applicable to all the other malignant tumors of the ovary.

Pseudomucinous cyst. A rather frequently occurring unilateral cyst of the ovary is the pseudomucinous cyst, so-called because it contains a mucinous fluid, glary and sticky, and which some chemists have said is not true mucin; consequently it has been described as pseudomucinous. In recent years, later studies indicate that this is a true mucin, and perhaps the term should be mucinous cyst. However, the former name is so deeply ingrained in the literature that it would seem most unlikely that one could change the term. The cyst most often is seen eight to ten centimeters in diameter when discovered, but may reach a very large size, filling the entire abdomen and causing a marked protuberance. Some cysts have been reported as weighing in excess of one hundred pounds, but in recent years they are rarely seen larger than a term pregnancy. The origin of the pseudomucinous epithelium is thought to represent a form of teratoma; it seems akin to intestinal epithelium and particularly the mucinous epithelium in the appendix, from which a mucocele may develop. The symptoms of the pseudomucinous cyst include pressure or enlargement of the abdomen. There may be slight or moderate discomfort. On occasion there is torsion of the pedicle, with sudden severe abdominal pain, nausea, vomiting and rigidity of the abdomen. The symptoms of torsion with this cyst are similar to that of torsion of any cystic or solid tumor of the ovary, or pedunculated myoma of the uterus. This cyst has a rather tough wall of white or pearl grey appearance, is fluctuant, and, as stated, contains a typical grey sticky glistening pseudomucinous or mucinous fluid. These cysts are seen particularly during pregnancy, or in the three or four months following delivery; one might wonder if there was some stimulation of these remnants in the ovary by the pregnancy hormones in these instances. The preoperative diagnosis can never be made. After the excised cyst has been opened and one finds the typical mucinous fluid, it is satisfying to know that malignancy is exceedingly uncommon in this type of cyst. Carcinoma is said to occur in three per cent of pseudomucinous cystadenomas. The thin walled unilocular cyst, without areas of thickening, is invariably benign. The cyst is rarely bilateral, and is not likely to recur. The condition of pseudomyxoma peritonei, the growth of pseudomucinous epithelium over the parietal and visceral peritoneum in the abdomen, is a strange one. This may be associated with the pseudomucinous tumor of the ovary, in which the epithelium has extended through the capsule and on to the surface of the peritoneum, or it may follow extension from the mucocele of the appendix. There is apparently no cure, and repeated laparotomy may be necessary to scoop out the pseudomucinous material; the thick, gelatinous fluid cannot be removed by paracentesis with any degree of success. Recently, Weed has sug-

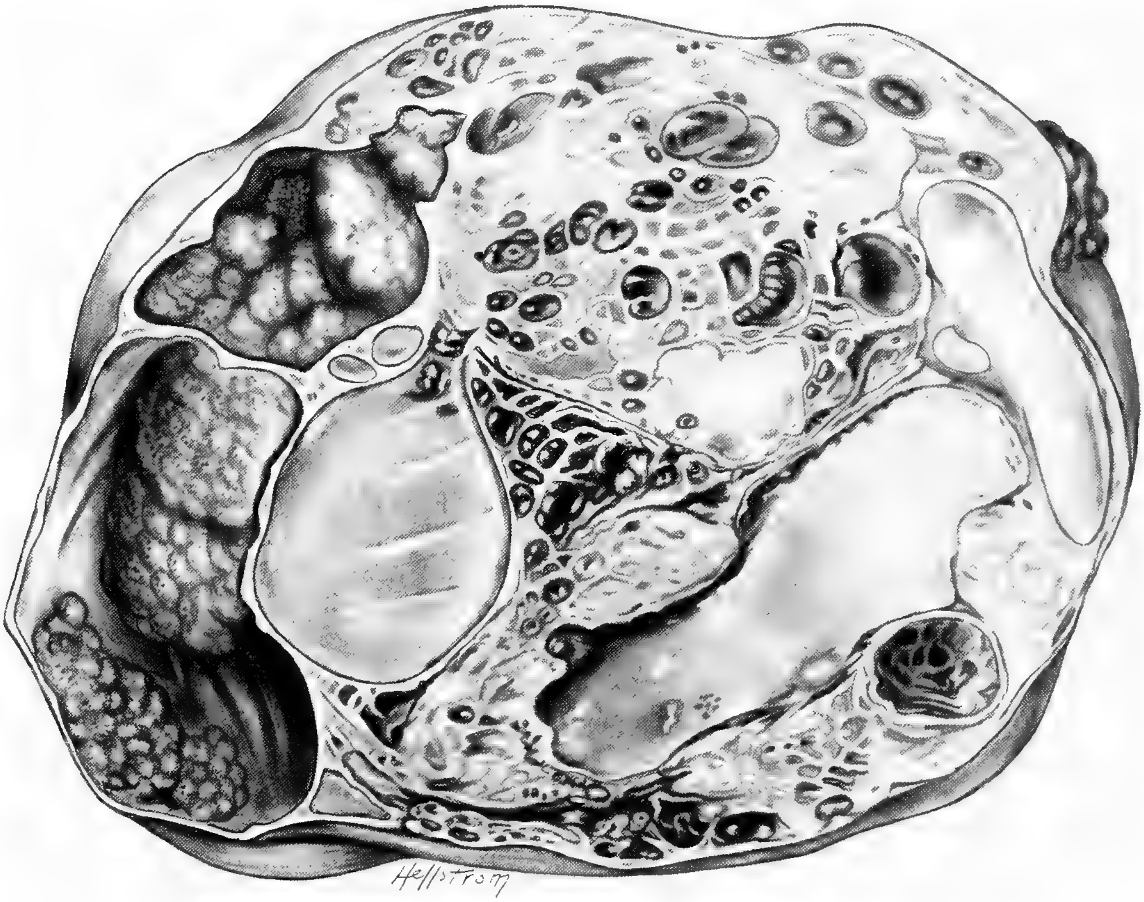


Fig. 233. Pseudomucinous cystadenoma. A benign multilocular cyst with areas of soft grayish tissue showing adenomatous glands. All cells are in single layer, very tall, with broad nuclei and cytoplasm distended with mucin.

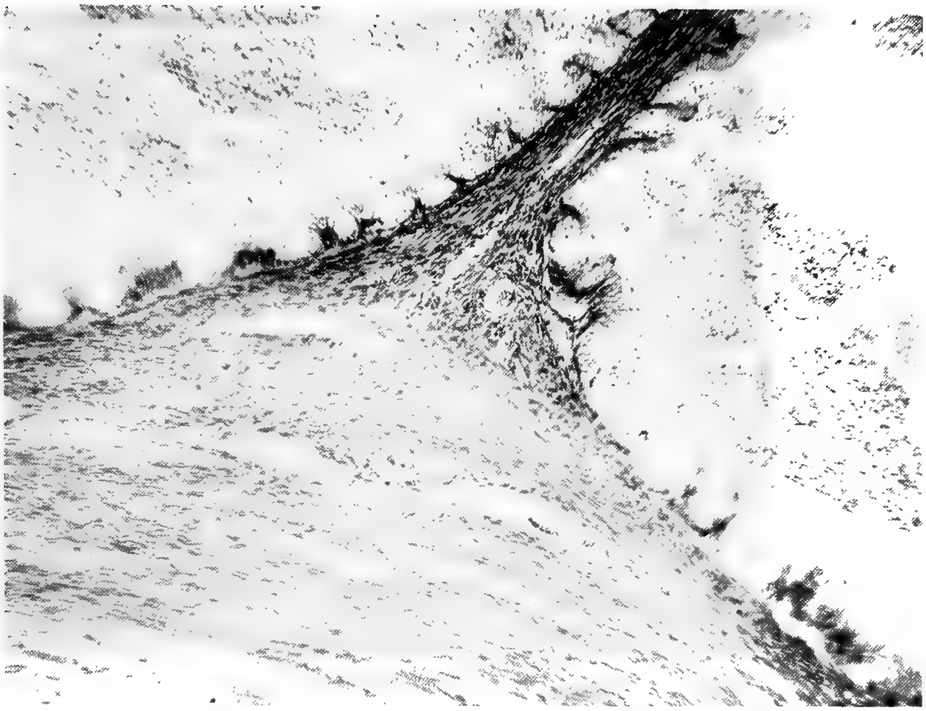


Fig. 234. Pseudomucinous cysts, multilocular, low power view. Within the interior of this multilocular cyst there are numerous small papillary arrangements covered over by a single layer of very tall mucin-secreting cells. A benign lesion.

gested the introduction of radioactive gold for treatment of this condition.

The pseudomucinous cystadenoma is more frequent in occurrence than the simple (unilocular) pseudomucinous cyst. This is a term ordinarily used for the multilocular pseudomucinous cyst. In the multilocular cyst, there are some quite large cavities and there are small cavities, some so small as to appear honey-combed, each little cavity being filled with pseudomucin, which may become thicker and congealed. The pseudomucinous cells may become closely packed together, so as to give an adenomatous appearance. Adenomatous changes may be confused with carcinoma. It is in these more solid areas that the adenocarcinoma of this particular type may develop. The histologic examination of the pseudomucinous cyst shows the lining to consist of a single layer of very tall columnar cells, containing a large clear globule which distends the length and end of the cell, pressing the small dark nucleus to its very base, and producing a very regular orderly appearance. Mitoses are rare. When carcinoma forms from this type of epithelium, the cells become closely packed together and tend to lose their pseudomucinous appearance, producing more of an undifferentiated or solid type of adenocarcinoma. Surrounding areas of the benign pseudomucinous epithelium may indicate the origin of the malignancy. These pseudomucinous cysts and cystadenomas usually completely replace the entire ovary and are rarely bilateral. In the walls of some of the pseudomucinous cysts there may be found small islands of Brenner cells, which are considered remnants of the wolffian duct system.

In the treatment of pseudomucinous tumors, conservative excision is the usual course. In the first place, the incision should be sufficiently large to remove the tumor without rupture or aspiration, if possible, but if there are extenuating circumstances such as a large cyst, that may be adherent or have a parastitic blood supply, aspiration may be

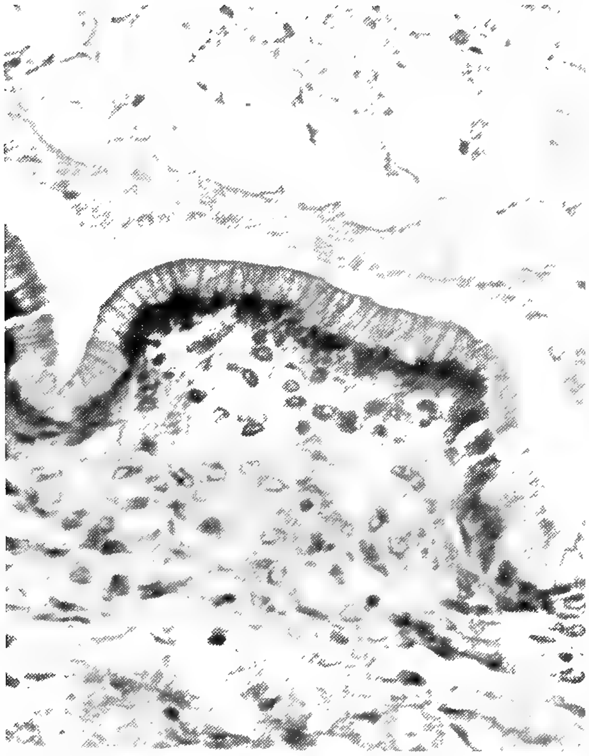


Fig. 235. Pseudomucinous cyst, high power view showing the lining of extremely tall columnar cells distended with mucus, which presses the nuclei to the base of the cells.

necessary after carefully damming off the area to prevent cells from falling into the interior of the abdomen. When the nature of the tumor is determined as being pseudomucinous, one is relieved to realize that the other ovary should be benign and not involved. In the rare case of pseudomucinous cystadenocarcinoma, if it could be determined by the fact that there was some extension through the capsule, some thickening in the ligaments, and some extension in the floor of the pelvis, the complete operation should be performed, removing the primary tumor, both tubes, ovaries and entire uterus. If there is any question of extension, postoperative deep x-ray therapy is administered. As said before, fortunately, malignancy with this cystic tumor is uncommon (three per cent).

The *primary solid adenocarcinoma* of the ovary is said to occur only half as frequently as the cystic adenocarcinoma. These tumors may be unilateral, but are bilateral in fifty per cent of the cases. The adenocarcinoma may be differentiated, very mature, or it may show varying degrees of undifferentiation, even to the medullary type. These tumors may be most variable in appearance microscopically. Undoubtedly many unclassified carcinomas are placed in this category of the primary solid adenocarcinoma. In fact, there are many individual tumors whose microscopic characteristics seem different from any other. These solid tumors may have small areas of cystic degeneration. As a rule, they are grayish or grayish pink in appearance, though they may appear yellow or reddened, and usually are smooth on the surface, but may be nodular. They may be soft, of brain-like consistency, or may be very hard (scirrhous). They probably arise primarily from the germinal or surface epithelium of the ovary, but it is possible that they may arise from congenital remnants or even forms of teratomas in the ovary. Undoubtedly, some of these adenocarcinomas arise in endometriosis; that is, the implants of endometrium in the ovary may become malignant, just as malignancy may occur in the endometrium of the uterus. There are a few recorded cases, in which it seems reasonable that the origin is endometriosis, but these are rare and seem much less frequent than the change of the endometrium of the lining of the uterus into malignancy. Novak has described the adenocarcinoma arising from endometriosis as frequently giving the appearance of the adeno-acanthoma, having squamous-like cells or squamous metaplasia cells within areas of the adenocarcinoma. This finding is suggestive but not conclusive of an origin in endometriosis.

The clinical diagnosis of the solid primary adenocarcinoma of the ovary is naturally difficult. A firm, moveable, nodular tumor to the side of the uterus may represent a pedunculated fibromyoma of the uterus, a fibroma of the ovary, or an ovarian carcinoma. When there is doubt as to the origin, ex-

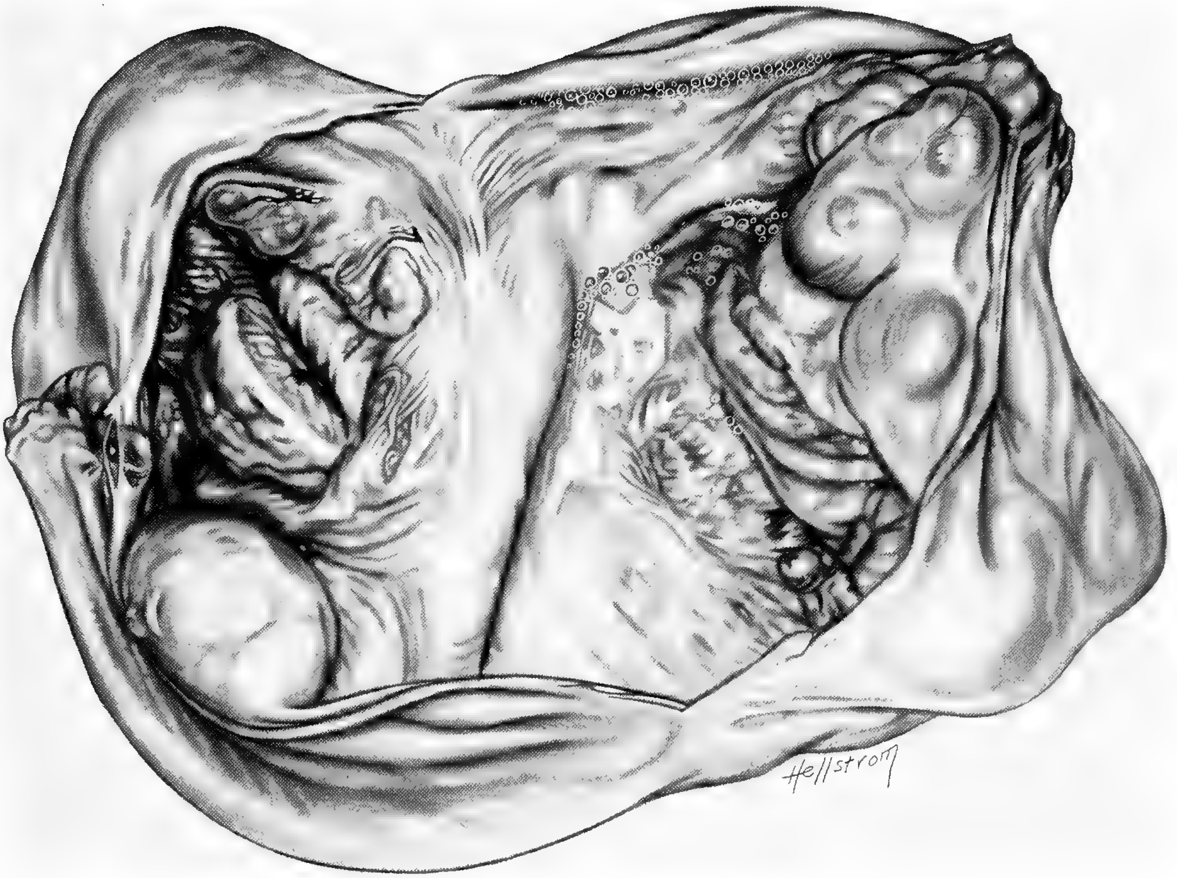


Fig. 236. Pseudomucinous cystadenocarcinoma. Some of the solid areas in this large multilocular pseudomucinous cyst show malignant change, the cells being multilayered, abnormal in appearance, and showing little mucinous secretion. Cured by excision.

ploratory surgery is indicated. While all malignant tumors of the ovary tend to occur in later life (sixty-three per cent occur after the menopause), it must be realized that they may occur in any age, including young children. The treatment is excision when possible, even when there is extension in the pelvis, and includes excision of the primary tumor and both ovaries. If there is extension in the pelvis, irradiation is indicated. If the extension is reasonably localized, a good result may follow intensive x-ray therapy. If the extension is throughout the abdomen, it is unlikely that any therapy will be of value. Chemotherapy, including thiotepa may be tried, but it is not a satisfactory treatment at this time. Radio-active gold is of questionable value. Studies in recent years do indicate that, even when the malignant tumor is apparently limited to one or both ovaries without extension, washings of the peritoneal fluid usually show the presence of cancer cells, and yet we know that a generous percentage of the patients are cured with surgical excision alone. This must mean that many of these floating cells are dead, or that the peritoneum has considerable immunity, or that the parent tumor is necessary for implantation of the

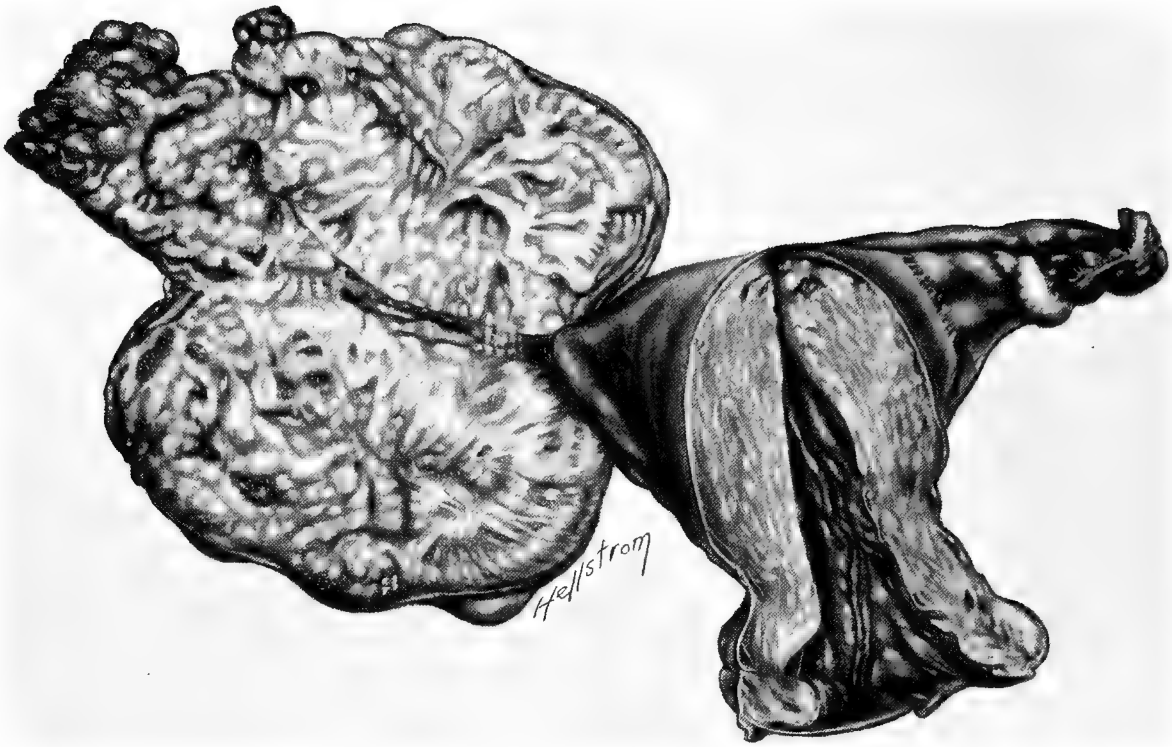


Fig. 237. Solid adenocarcinoma of ovary, clear cell type. Age 58 years. A yellowish, granular, firm, adherent, fixed tumor with extension to local tissues. Cured after excision and intensive x-ray therapy. Two years later developed intestinal obstruction, had resection of bowel. Well after eight years.

cast-off cells. Because these cells have been found floating in the peritoneal fluid, certain long-term experiments are under way, which include the introduction of radio-active gold or chemotherapeutic compounds in the peritoneal cavity at the time of surgery. A similar diffusion of cells is found in the peritoneal cavity of patients with carcinomas of other origin, particularly that of the stomach and bowel, as shown by washings made at the time of surgery.

Secondary or metastatic carcinoma of the ovary. The ovary is a fertile field for metastatic tumors; carcinoma cells from almost any place in the body may find their way to the ovary, and grow well. The metastatic tumors include four types; the *cystadenocarcinoma, the solid adenocarcinoma*, the *Krukenberg tumor,* and *miscellaneous carcinomas.* The most frequent secondary tumor is probably the *cystadenocarcinoma* of the serous type which occurs in one, or often in both ovaries, and may be metastatic from carcinoma of the endometrium, the sigmoid, various other areas of the colon, the stomach, the pancreas, and other organs. From fifteen to eighteen per cent of all cases with adenocarcinoma of the endometrium metastasize to one or both ovaries. If the metastasis is present long enough, a well marked cystadenocarcinoma may be formed. These secondary tumors are treated by excision. Often, one does not real-

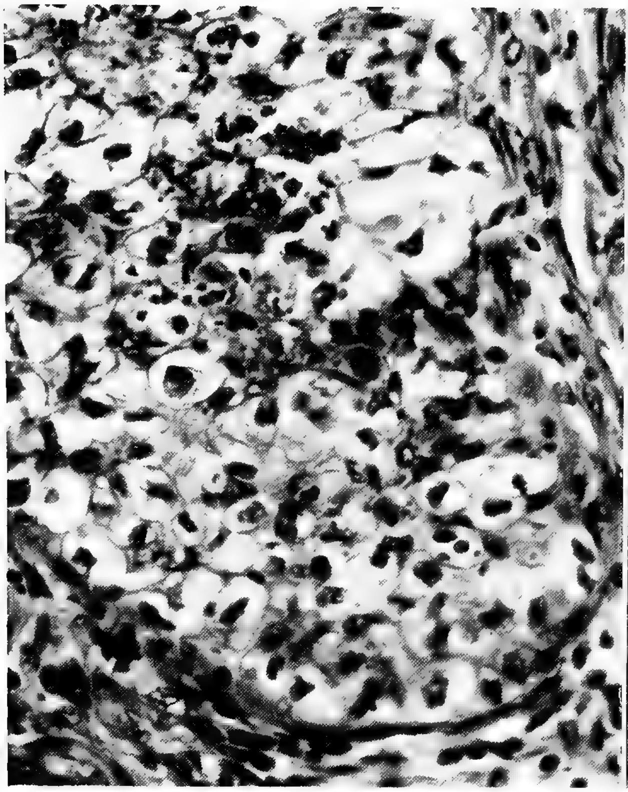


Fig. 238. Primary solid adenocarcinoma of the ovary, clear cell type. The distended vacuolated tumor cells have a rather clear appearance although the nuclei are quite irregular in size and shape and masses of chromatin are scattered in the cytoplasm of the cells. This tumor had extended onto the local peritoneum, but was cured after excision and intensive x-ray therapy. (From case in Fig. 237.)

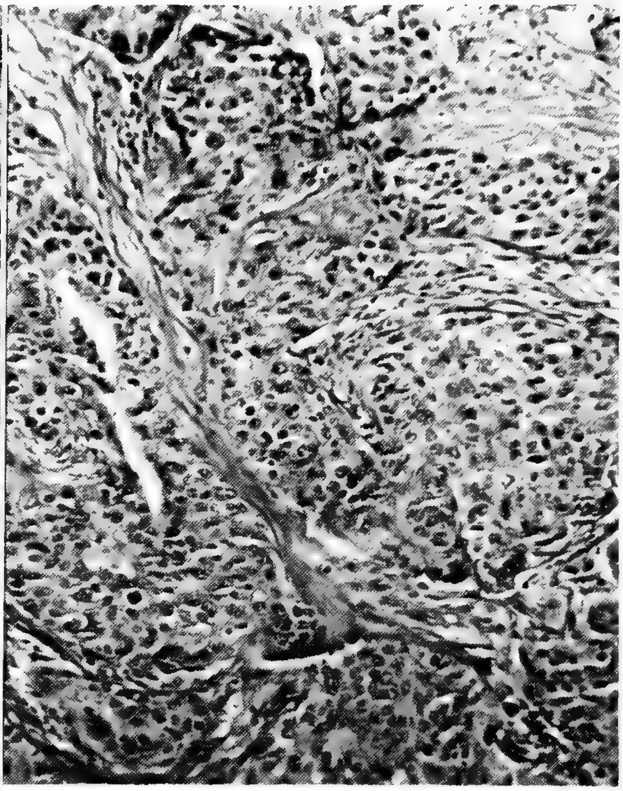
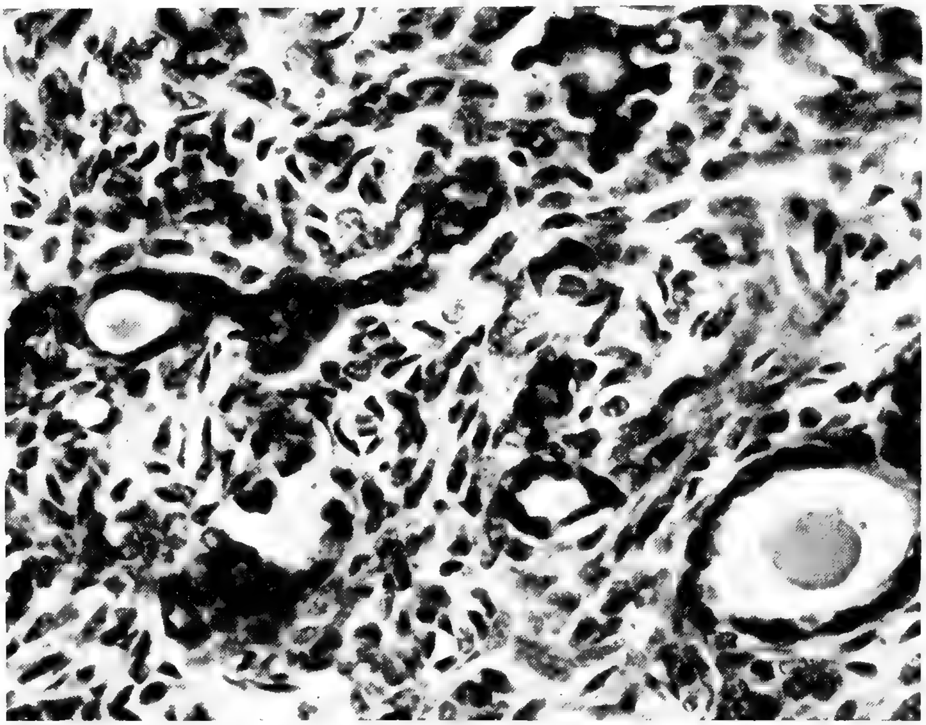


Fig. 239. Primary solid adenocarcinoma of ovary. Medullary type.

ize they are secondary until after removal. The true origin may be determined later by finding the carcinoma in the bowel wall, the endometrium, or elsewhere. If there is metastasis from the bowel, naturally one could not expect a cure; when there is metastasis from the endometrium, the possibility of cure does exist after complete excision.

The *solid adenocarcinomas of metastatic origin* may come from the bowel, stomach, and various other organs, including the pancreas and breast, and may have a pattern suggestive of their origin, but often the tumor is undifferentiated and not distinctive. The third type of secondary carcinoma is the Krukenberg tumor. This tumor is a distinct type of metastatic tumor, and by definition indicates a *mucin-secreting* metastatic carcinoma. This mucin-secreting tumor arises most of the time from the stomach, less often from the colon, and in rare instances from other organs, such as the gallbladder and breast. There are a very few reported cases of primary Krukenberg tumor of the ovary; such reports are always somewhat suspect, but apparently the primary type can occur. The Krukenberg tumor, as a rule, is a bilateral solid growth, quite firm, lobulated, with well-developed capsule. Occasionally it has a spongy appearance, and may show cystic degeneration with gelatinous material in the center. Occasionally, these metastatic tumors may be truly cystic. The microscopic characteristics are definite, the first of which is the *melting-down* of glands, in which the adenocarcinomatous glands seem to break open and the cells gradually blend into the stroma. This melting-down has a unique appearance. The second point is the presence of

Fig. 240. Krukenberg tumor of the ovary. The melting down of glands in this secondary mucinous carcinoma, metastatic from the stomach or colon, is shown with the tumor cells extending out into the stroma. Some of the glands are dilated. The nuclei are quite irregular in the tumor cells. Often there are dilated signet-ring cells present, but none are shown in this section.



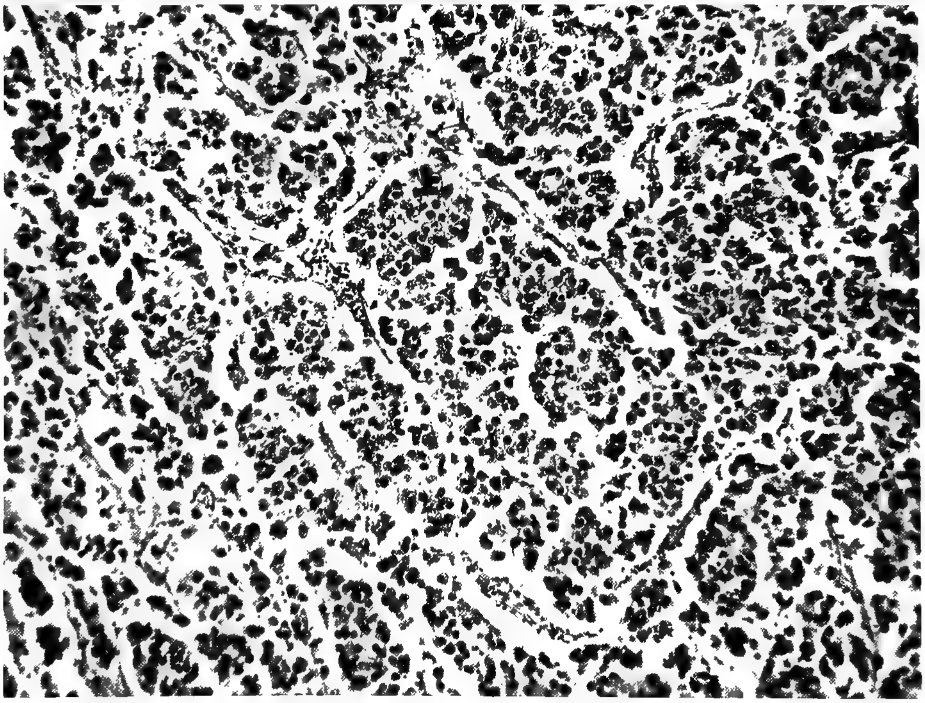


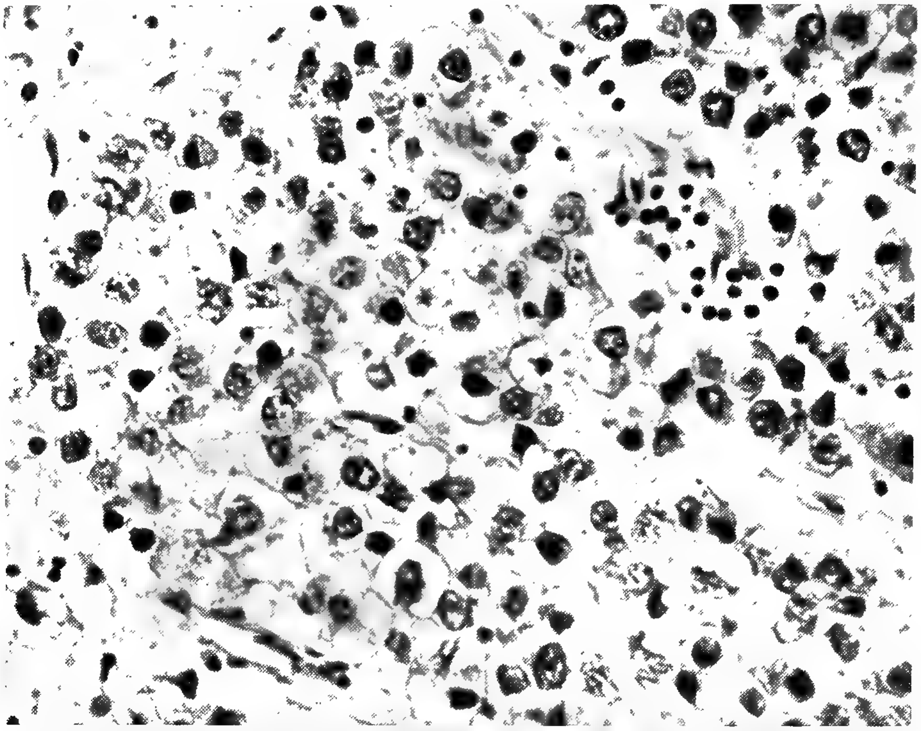
Fig. 241. Dysgerminoma of the ovary, low power view. The areas of tumor cells, here somewhat separated in their fixation, are grouped together within thin septa containing a peppering of lymphocytes. These tumor cells show irregularity in the nuclei and indicate malignancy.

the *signet-ring* cell. These individual cells may be scattered throughout the stroma of such tumors, being rather large, having the flattened nucleus displaced far to one side of the cell, while the cytoplasm is greatly distended by unstaining mucous (in the ordinary hematoxylin and eosin stain). With special mucin stain, the cytoplasm has a brilliant color. As to the origin of Krukenberg tumors, it is felt that they likely develop by retrograde lymphatic metastasis, though they may arise from peritoneal implants from tumor cells which pass through the surface of the stomach or other organ and are carried by the peritoneal fluid to the ovary. However, the fact that the original tumor commonly has not penetrated the serosa at the point of origin and the fact that the metastatic tumor seems to develop in the very center of the ovary mitigates against the peritoneal implant theory. The possibility of implants through ovulation openings has been suggested. Blood stream metastasis always must be kept in mind. It is evident that the ovary is a very fertile field for metastatic cancer cells. Possibly the cells metastasizing through the blood stream simply arrive at this destination, where they are nourished and encouraged to grow more rapidly than they may be encouraged to remain in other areas in the body. It is interesting that the secondary tumors often overshadow the primary tumor, growing much more readily in the ovary. One may think that the tumor is limited to the pelvic organs, later to find the origin in a different area. Sometimes the very marked stromal reaction in these cases may suggest sarcoma. *Miscellaneous carcinomas* that may metastasize to the ovary include those squamous cell carcinomas and adenocarcinomas from any part of the body, because the ovary is such a fertile field in which metastatic tumors may grow.

DYSONTOGENETIC TUMORS

Dysgerminoma. The next group of tumors, of which the dysgerminoma is the lead-off type, may be called the dysontogenetic tumors. Their definition and clarification have resulted from the work of two great gynecologic pathologists, the first, Robert Meyer of Germany, who did so much to clarify the origin of these tumors, and the second, Emil Novak of Baltimore, who helped to explain and to bring their meaning to all English-speaking people, after studying and reporting large groups of these tumors. To understand the origin of the dysgerminoma and the other dysontogenetic tumors requires some knowledge of the embryology of the ovary. In early embryonic life, when the celomic cavity is formed, there are gathered together in one portion of the dorsal part of this cavity a group of quite undifferentiated cells, known as the sex cells which form the sex ridge. It is from some of these very undifferentiated cells, which may remain in the ovary after birth, that the dysgerminoma may develop. A cell that is not yet identified with male or female elements forms a tumor which may occur in both the male and female gonad. In the male, this tumor occurs not uncommonly and is called the seminoma of Chevasseu. In the female, the name of this tumor is well identified with the word dysgerminoma, and this is the common appendage. It is interesting that the tumor seems somewhat more likely to develop in the individual with abnormal gonadal development, as a pseudohermaphrodite, who may have an absent vagina, absent uterus, or some other form of congenital abnormality in the pelvic organs. But this is not necessarily true, because half of the cases show no developmental defect at all. This tumor may occur in the very young, during menstrual life, or after the menopause. It is a doughy, rubbery, solid tumor of grayish or pinkish-gray appearance, which may have some yellowish areas, and may show areas of necrosis, hemorrhage or degeneration. It is usually unilateral. Some

Fig. 242. Dysgerminoma of the ovary, high power view. Here the large, ovum-like cells have vesicular nuclei in many instances. Many others are quite dark and irregular. The increased mitoses and the irregularity of nuclei indicate malignancy. Within the delicate stroma are collections of lymphocytes.



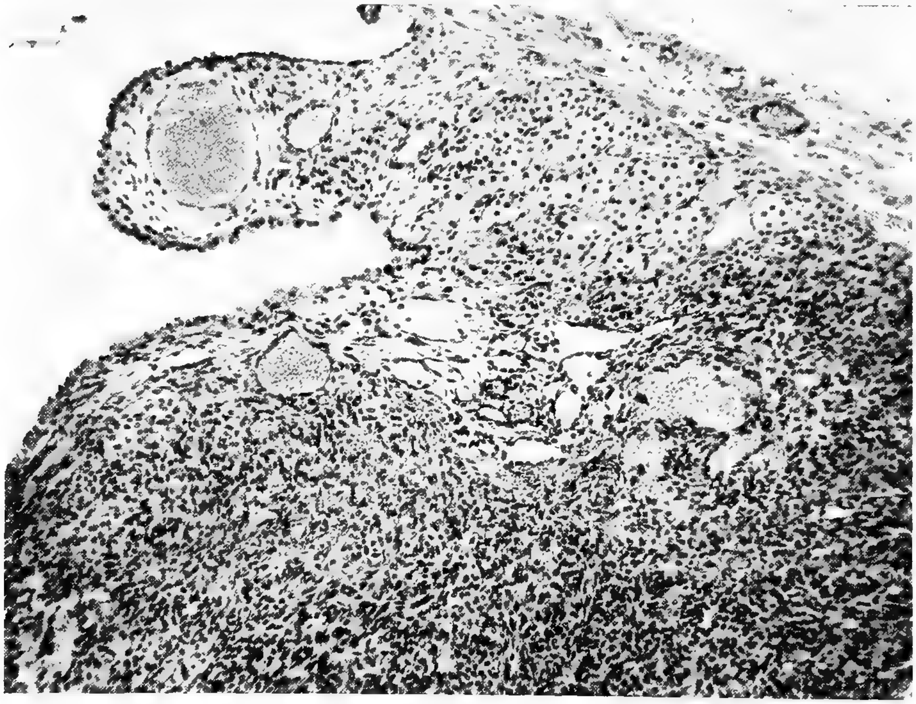


Fig. 243. Arrhenoblastoma of the ovary. The inferior portion of the photograph shows a fibroma-like tumor with a tendency to form strands of cells which represent the extremely immature testicular tubules. The upper central portion of the photograph shows the larger pink-staining interstitial cells of Leydig, which are responsible for the secretion of androgen from this tumor.

degree of ascitic fluid is usually present. If the tumor is freely moveable with no adjacent induration, peritoneal implants, or enlarged lymph nodes, one may think that it is a benign tumor, and unilateral excision is indicated. If there is evidence of extension onto the pelvic peritoneum or even metastasis in some pelvic lymph nodes, more often one would perform a complete operation removing the uterus, tubes and ovaries. Certainly, if the second ovary seemed to be involved, one would remove the entire pelvic organs. Novak has stated that about thirty-seven per cent of the cases appear to be malignant, the remaining two-thirds being benign. This is determined by the appearance of the tumor microscopically. There are distinct microscopic characteristics. The cells are quite large, closely packed together, having a pale cytoplasm with large nuclei, rather vesicular in appearance, so that these tumors have been described in the past as ovum-cell tumors, because the cells simulate ova. Also, it has been called the large-cell carcinoma. Mitoses in these cells are some indication of the degree of malignancy. If there are no mitoses, or if they are rare, one would assume that the tumor is benign. If there are numerous mitoses, particularly of the abnormal type, with irregular masses of chromatin, the tumor is malignant. Surrounding groups of these large cells which form this tumor, there are fine delicate septa of connective tissue, within which there are a scattering of small lymphocytes. These minute cells appear as grains of pepper in the delicate stroma of the septa, and add to the characteristic appearance of this tumor, which is so readily diagnosed under the microscope. It is of particular interest that this tumor as a rule is *sensitive to x-ray therapy,* which gives a hopeful prognosis, even though it has extended or metastasized. Ordinarily, the amount of x-ray therapy needed to produce a prompt regression of the growth is relatively small. Experience has shown that the tumor may recur, and that further treatment may be necessary at intervals through succeeding years. Not all of these tumors are sensitive to irradiation therapy, and some will continue to grow in spite of this treatment, with progressive extension and death. If the tumor were only partially removed and x-ray therapy were given, one would think that the remaining otherwise normal ovary would be permanently destroyed by deep x-ray therapy. However, there is one report in the literature of a case in which the patient had a full amount of x-ray therapy for a pelvic tumor in childhood, and a number of years later reached puberty and developed normal menses. This suggests that the prepubertal non-functioning ovary may be more resistant to irradiation than the adult functioning ovary. Before accepting this, much more information is needed.

Arrhenoblastoma. When the embryo is about six weeks of age, a male sex wave develops in the sex ridge, in every individual embryo. This male sex wave consists of the development of sex cords, or columns of cells, which grow in the hilum of the mass of cells to form a medulla. These cords may anastomose one with the other, and represent the earliest primordial development of the seminiferous tubules of a testis. This male sex wave remains in a status quo for a period of time. After a few weeks, it may progress in further masculinization and form the seminiferous tubules of a testicle. Or from some undetermined source there may develop a female sex wave, superimposed on the male sex wave, to develop the cortex that subsequently will become an ovary. In these circumstances, the embryonic cords are pressed towards the hilum of the gonad, where they become more differentiated as the rete ovari in the adult ovary. It is thought that some of these undifferentiated cords may develop into tumors of the ovary in adult life, forming the arrehenoblastoma, the name given by Robert Meyer.

The microscopic appearance of the arrhenoblastoma is variable. On the one hand, there is an adult form of tumor called the testicular adenoma of Pick, in which there are large tubules, containing a single layer of large cells, having a somewhat frayed internal border, which are suggestive of the seminiferous tubules of the testis. This adult type of tumor does not secrete any hormone, has no secondary sex changes, and is benign as a rule. The less differentiated types do secrete androgenic hormones. These include the tumors which have the fibrous tissue background with cords, some of which may have small cavities or tubule formation. More often the cords of small dark cells can be seen to extend around through the stroma of the tumor and to show nuclei transverse to the long axis of the column; this has been pointed out particularly by Novak. Also, within the connective tissue stroma there are interstitial cells, which are relatively large, having a pink or pink-red appearance, similar to the interstitial cells of Leydig in the testis. It is thought that these are the cells which secrete the male hormone. In some tumors, the appearance is that of a fibroma or sarcoma of the ovary, and very many sections may be examined under the microscope before cords or the interstitial cells can be found. Because of indistinct changes in the microscopic appearance of the arrhenoblastoma, the correlation of the history of the patient is frequently necessary in diagnosing this strange masculinizing tumor.

These tumors are rare, and yet are not unknown in most pathology laboratories. They usually occur during menstrual life, most often between twenty and thirty years of age. A patient who develops such a tumor first notices amenorrhea. After three or four months of amenorrhea a growth of hair appears on the face, arms, legs and abdomen, and around the nipples of the breast. At the same time, there is loss of fat pads around the hips, and the breasts become atrophic. The clitoris becomes distinctly enlarged to two, three or four centimeters long, and one and one-half or two centimeters in diameter. This represents defeminization followed by masculinization. Examination of the patient may reveal a tumor mass to the side of the uterus, usually not large, perhaps the size of a lemon, occasionally the size of an orange or a grapefruit. When a tumor is palpated under these circumstances, the indication for surgery is clear. If the urine is analyzed for 17-ketosteroids, this metabolic product of androgens is present in increased amount. Up to twelve milligrams for twenty-four hours is considered normal. With this tumor, twenty or thirty milligrams are present, and sometimes fifty or one hundred milligrams. Androgens may be produced in increased amounts by adrenal cortical hyperplasia and adenoma or adenocarcinoma of the adrenal cortex. Thus, there may be a distinct difficulty in making the diagnosis. If there is no palpable tumor in the pelvis (and proper examination may require general anesthesia), one would assume that the difficulty more likely was in the adrenal gland. Adrenal visualization is possible in x-ray films, after the injection of air, oxygen, or carbon dioxide through a needle in the perirenal space, or after injection anterior to the sacrum and beside the rectum into the retroperitoneal space, allowing the air or gas to find its way up to surround the kidneys and outline the adrenal glands. Films may indicate adrenal hyperplasia, or may show clearly the outline of an adrenal tumor on one side or the other. Certainly if one can palpate a tumor in the pelvis, exploratory laparotomy is indicated.

The arrhenoblastoma has a grayish, yellowish, firm appearance, and may contain some cystic cavities. Twenty-five per cent are said to be malignant and the remainder benign. Because of the probabilities, conservation is in order and removal of the involved ovary only is indicated, unless there is obvious extension in the pelvis.

This tumor may produce no local discomfort but may be suspected or palpated, or discovered at exploratory operation. As a rule, local conservative excision is indicated, unless the tumor is obviously invasive, when radical surgery is indicated. If local excision can be

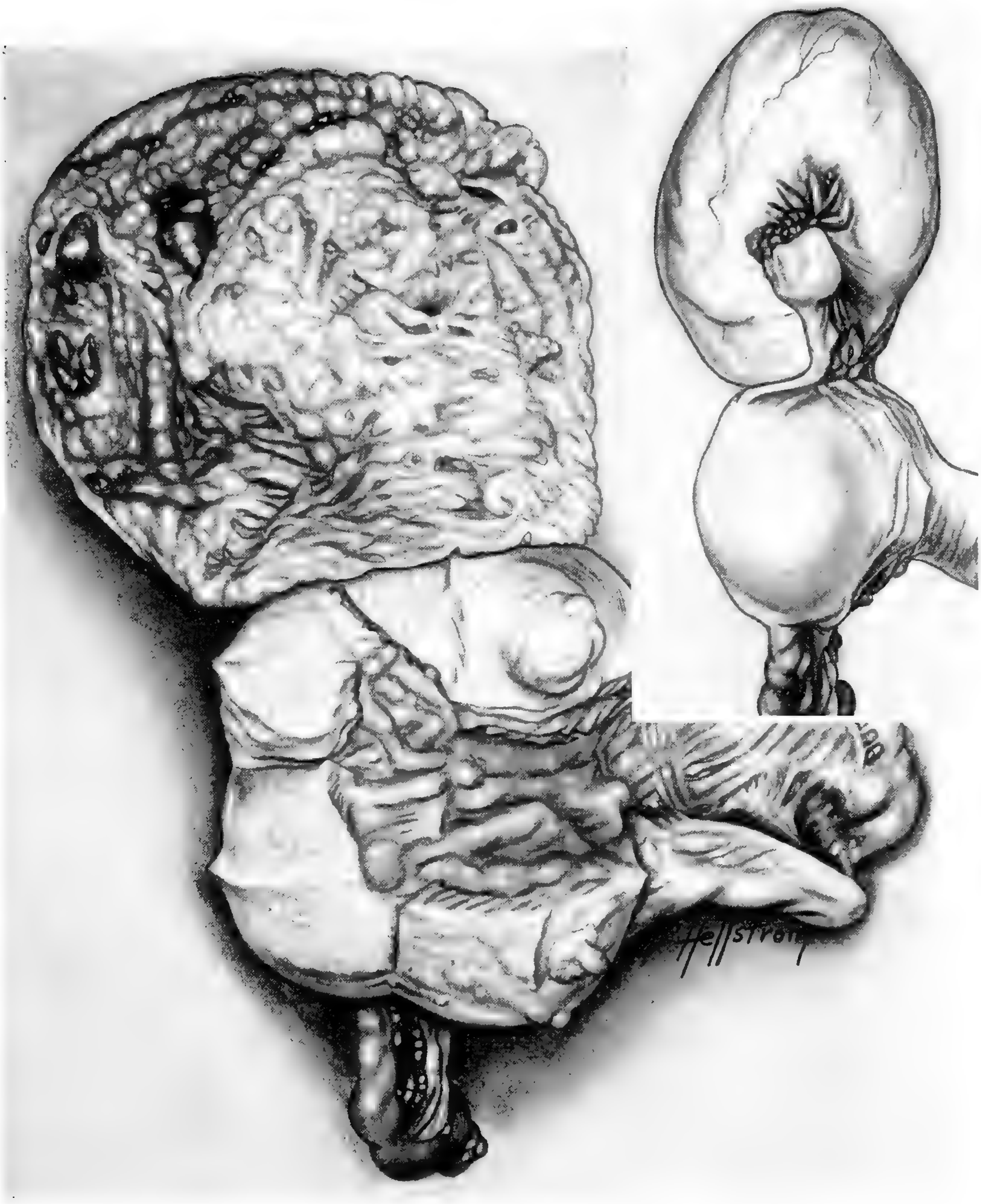


Fig. 244. Benign granulosal cell tumor. Age 64 years. A granular rubbery tumor of yellowish color and with slight cystic formations. Small myoma of uterus, marked endometrial hyperplasia, post-menopausal bleeding. Cured by excision.

performed, remarkable regression may follow. In two or three months the menses may be re-established, breasts enlarge, fat pads be restored, voice return to normal, much of the hair disappear, and fertility return.

The *granulosal cell tumor* is another extraordinarily interesting tumor, more frequent in occurrence than the two previously mentioned dysontogenetic tumors. It is thought to arise from the pro-granulosal cells, which are the embryonic cells that appear in the female sex wave which spreads over the foetal gonad at about the age of three months. From the stromal cells of the early gonad, there develop primary germ cells, or oogonia, surrounded by cells which are the progenators of the granulosal cells. It is thought that the latter may remain as rests in the ovary after birth, from which granulosal cell tumors may develop. This is the theory of Robert Meyer. The pro-granulosal cells and the pro-thecal cells have a similar origin from the ovarian mesenchyme or the connective tissue of the ovary. It is natural that the granulosal cell tumors and thecomas are closely related, that they frequently have a connective tissue appearance, and that the stromal background may be prominent in them. The granulosal cell tumors secrete estrogens in varying amount; some evidently are much more potent in this respect than others. Also, the effect of these tumors is more dramatic and more obvious in the prepubertal child, and in the postmenopausal woman. In the prepubertal child, the breasts and vulva enlarge, genital hair appears, and there is vaginal bleeding which may be cyclic. Precocious menstruation always brings to mind the possibility of a granulosal cell tumor; the appearance of a pelvic tumor may clarify the origin or cause of such precocity. Shortly after the granulosal cell tumor was described in this country in 1931 by Robert Meyer, there was much enthusiasm for this diagnosis, and any child with precocious puberty, especially those who were very young, were always suspect of having this

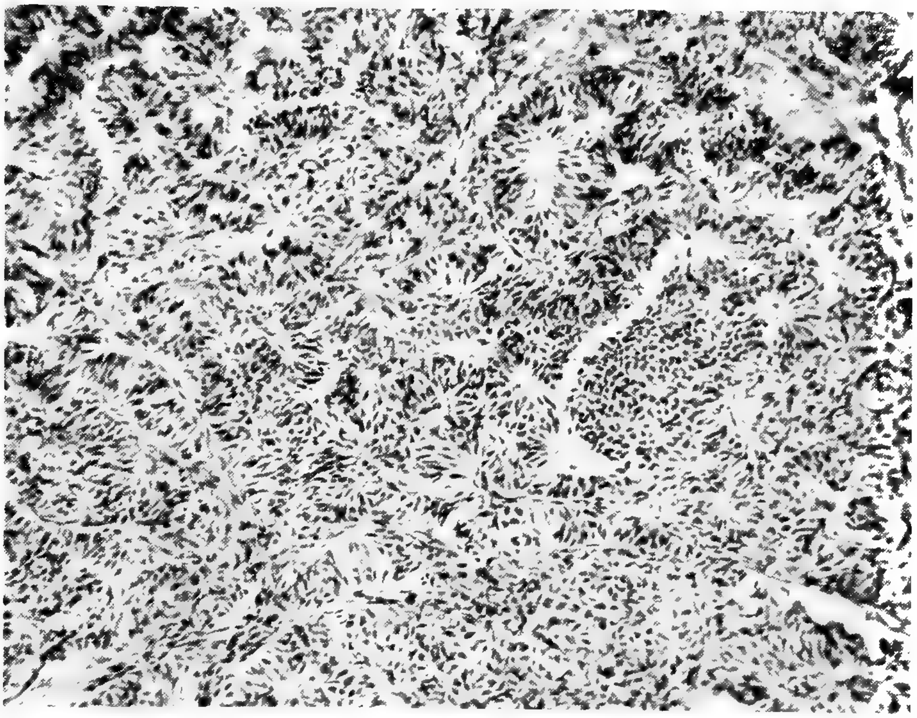


Fig. 245. Granulosal cell tumor of the ovary. The granulosal cells are arranged particularly in broad columns and form rosettes, in the center of which there may be present inspissated material, known as Call-Exner bodies.

tumor, and probably most of them were explored. The majority of times there was no tumor. Now it is realized that the majority of the cases with precocious puberty have truly precocious stimulation from the hormones of the pituitary gland and ovary, and no granulosal cell tumor. At the present time, unless a tumor is palpable, one would prefer not to explore the abdomen of these children, although they should be kept under careful observation at regular intervals. The feminizing effect after the menopause also is very obvious. The woman of fifty, sixty, or seventy years of age develops firmness in her breasts, feels a spring in her step because the hormones make her feel better, develops a thick vagina, and is surprised by vaginal bleeding which may appear cyclically. She may think she has found the fountain of youth, only to be disillusioned by the palpation of a mass in the lower abdomen, indicating the tumor. When a tumor is palpated by the physician, surgery always is indicated. Sometimes these tumors are very small and difficult to feel. As stated with the prepubescent child, at one time the complaint of postmenopausal bleeding, especially when associated with endometrial hyperplasia, stimulated the strong suspicion that a granulosal tumor must be present, and many women had exploratory operations, searching for small tumors that were rarely found. Endometrial hyperplasia in its marked form, from apparent hyperestrogenism, may occur long after the menopause, without any granulosal cell tumor of the ovary. These late estrogens may come

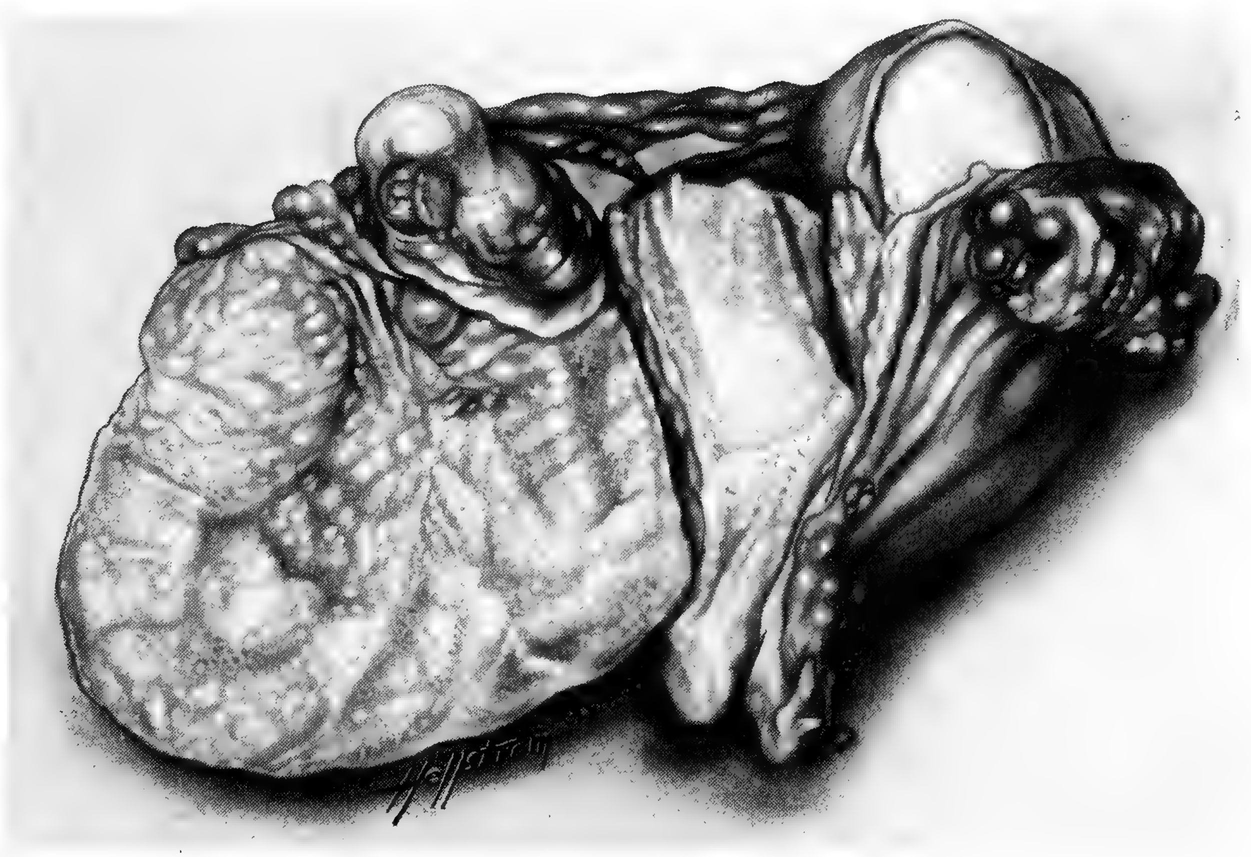


Fig. 246. Granulosal cell carcinoma. Age 62 years. Yellowish, granular tumor, adherent, with implants on local peritoneum. Myoma in fundus, slight postmenopausal bleeding. Slight endometrial hyperplasia. Intensive x-ray therapy. Cured 4 years.

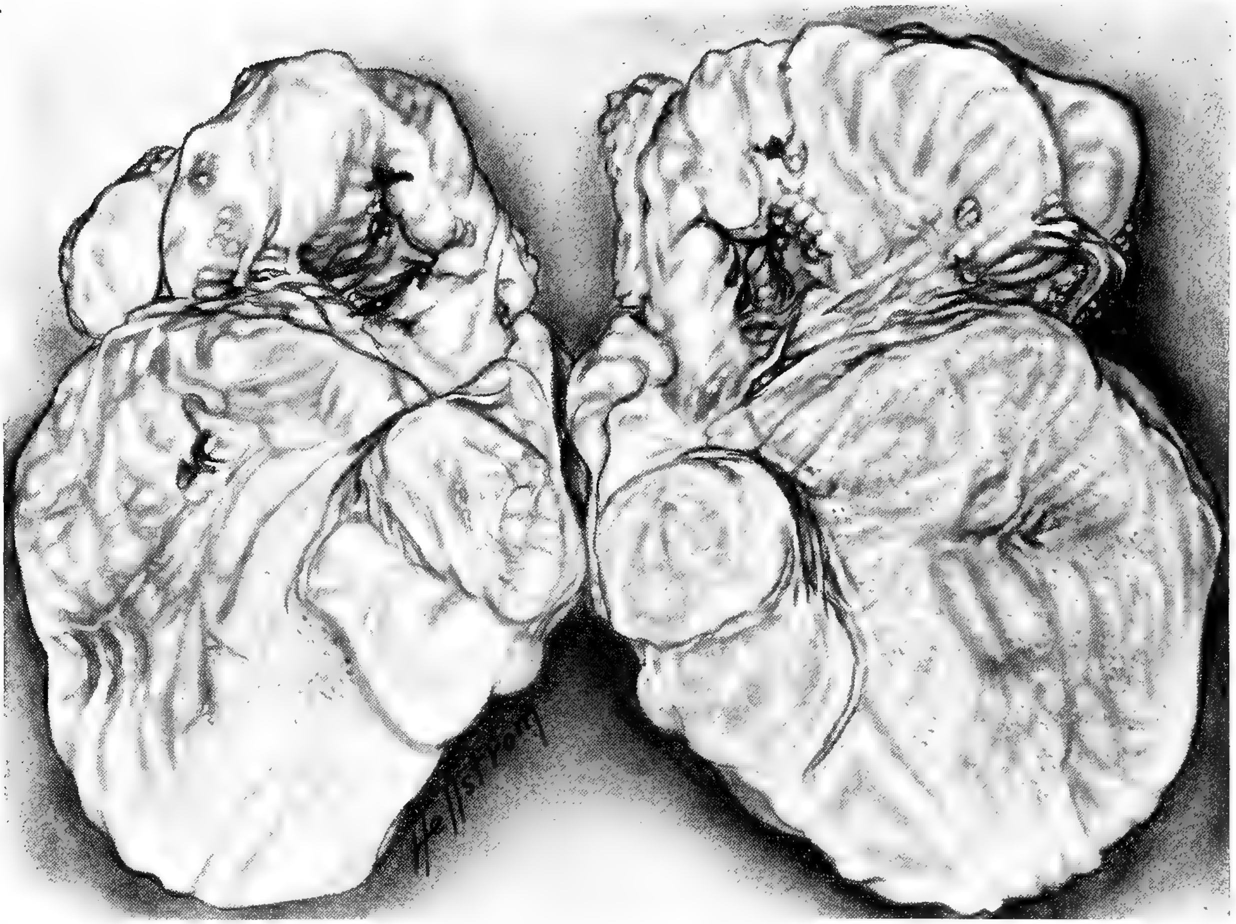


Fig. 247. Thecoma of ovary. A yellowish, quite firm, fibroma-like tumor, containing doubly refractile fat in tumor cells. Associated endometrial hyperplasia and post-menopausal bleeding.

from the ovary itself (at times there are small cysts present apparently functioning long after the menopause) or perhaps from the adrenal cortex. At any rate, now the abdomen is not explored unless there is recurrence of bleeding; then operation may be indicated, not particularly to look for the granulosal cell tumor, but because recurrent postmenopausal bleeding, associated with endometrial hyperplasia, not relieved by one or two curettages, may be followed by the subsequent development of endometrial carcinoma.

The gross appearance of the granulosal cell tumor is that of a firm or rubbery tumor which may be lobulated and solid, or partly cystic, or it may contain large cystic areas. Commonly, it has a somewhat yellowish color. There may be areas of brownish or hemorrhagic necrosis, such as occurs with all types of tumors, due to interference with their blood supply. The tumor may be freely moveable, may be adherent, or may have extended onto the pelvic peritoneum and over the surface of the surrounding organs. The microscopic appearance of the granulosal cell tumor is much more characteristic than that of the arrhenoblastoma, but does have a variable appearance. The most characteristic form is the follicular type, in which there are solid masses of granulosal-like epithelial cells, small, bluish, and usually homogenous. They form small rosettes of cells that are gathered around a minute cavity or a blood vessel, usually a cavity, in a center of which there may be congealed material. These are known as Call-Exner bodies. In the rosettes the cells are arranged longitudinally, pointing toward the cavity; this is characteristic. Cystic spaces may occur, surrounded by masses of granulosal cells. Connective tissue stroma is quite prominent in some areas, and quite sparse in others. When the tumor is benign there are rare mitoses; when it is malignant the mitoses become very frequent and may look quite abnormal, with giant nuclei or irregular masses of chromatin. Novak has pointed out that around the small structures the nuclei of the inner layer of cells are very close to the central lumen, while the outer layer of cells has nuclei away from the lumen. There has been described also the diffuse or parenchymatous type, the cylindromatous type, and a gyriform type of granulosal cell tumor. Another variation of the granulosal cell tumor is the *thecoma,* a tumor of fibrous-like tissue, so much so that it may appear to be a fibroma or perhaps a low grade sarcoma. Actually this tumor is somewhat more malignant than that of the granulosal cell tumor itself. Of the latter Novak has estimated that twenty-eight per cent are malignant. This tumor is distinguished from the connective-tissue tumors by the presence of doubly refractile fat globules in the cells. It is felt that these cells arise from the pro-thecal cells of the ovary. This tumor also may secrete estrogen, as the granulosal cell tumor may. Both granulosal cell elements and evident thecal elements may be found together in the same granulosal cell tumor. This again argues for a common origin, at least in the remote embryologic sense, and this is the reason for classifying them together. Another relative of the granulosal cell tumor is the very rare *luteoma,* a tumor of lutein cells, which is a form of the granulosal cell tumor, which has been changed by an endocrine stimulus. These small yellowish tumors evidently may secrete progesterone, because they have been described as being associated with progestational endometrium. They occur very rarely.

As regards the endometrium associated with the granulosal cell tumors one would expect an endometrial hyperplasia pattern in the majority of cases, and this is true. The appearance is that of "swiss-cheese" hyperplasia with thickened endometrium, large cystic glands, and very tall non-secretory epithelial cells, producing no glycogen, typical of hyperestrogenic endometrium. In ten per cent of all cases with granulosal cell tumors of the ovary, there is associated adenocarcinoma of the endometrium. Apparently this adenocarcinoma develops from the endometrial hyperplasia. This is one reason for suspecting the hyperplastic endometrium may be a precancerous lesion in some instances, and for suspecting that estrogens may have a causal relationship. Two tumors may occur coincidentally, but one can hardly believe this is true in this instance. As a rule, with the granulosal cell tumor, one would wish excision of the uterus because of endometrial carcinoma, except for the fact that two-thirds of these ovarian tumors are benign. In young women, one probably will choose to chance a final benign diagnosis and hope that the patient will be able to maintain her fertility. That seems to many practitioners of the art to be the most important purpose of the gynecologist. On the other hand, extremely close follow-up of such a patient should always be made, if the conservative surgical approach is used. When the tumor has extended beyond the ovary, often it is insensitive to irradiation therapy. Because of the connection of the granulosal cell tumors, the thecoma, and the luteoma, Novak has suggested that they all be grouped together as *feminizing mesenchymomas* of the ovary.

Gyandroblastoma is a very rare tumor. It contains both female and male elements. This tumor appears in some areas to represent the granulosal cell tumor, and in other areas to represent the arrhenoblastoma. It is said that the masculinizing effect is usually predominant. This tumor is usually malignant, and, as stated, is very uncommon.

OTHER MASCULINIZING TUMORS

The *masculinovoblastoma* or *adrenal tumor of the ovary* arises from adrenal cortical cell rests in the ovary. From these cell rests, there may develop an adrenal tumor, which is similar to the functioning cortical tumor of the adrenal gland, and which may cause masculinization. There is increased 17-ketosteroid excretion, much more than with the arrhenoblastoma, which may show no elevation. This tumor may be benign or malignant; more often it is malignant. It first causes defeminization, and then masculinization, as with the arrhenoblastoma. The administration of cortisone does not reduce the 17-ketosteroid excretion, acting as the adrenal cortical tumor does. It again is a rare tumor.

The *hilus cell tumors* have been described in recent years and also are rarely occurring masculinizing tumors. These tumors arise from islands of the sympathicotropic or hilus cells, which are identical with the Leydig cells, so considered because these cells contain the Reinecke crystals, which appear as rectangular masses in the nuclei of these cells. Very few of these tumors have been reported. Steinberg notes that cell rests are more frequent than the tumors, and that even very small masses of these cell rests may be virilizing. Very little is known regarding this condition.

NON-HORMONE SECRETING TUMORS OF DEVELOPMENTAL ORIGIN

The *Brenner tumor* is a fibroma-like tumor, containing cell rests of Walthard, which are masses of indifferent cells, somewhat suggestive of squamous cells, but which usually have

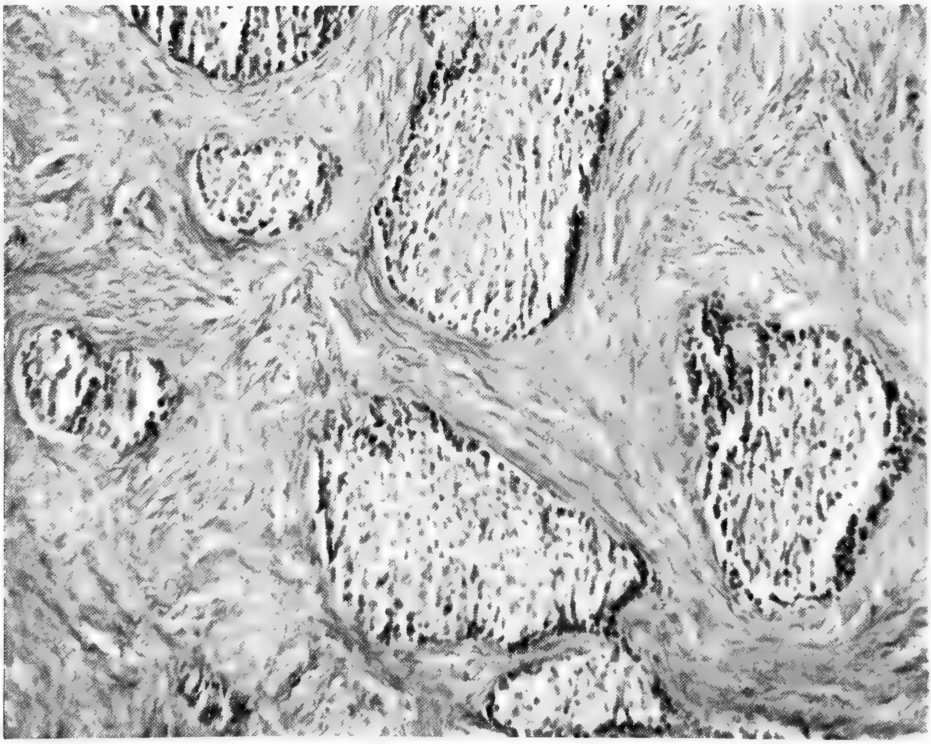


Fig. 248. Brenner tumor of the ovary. A fibroma-like tumor with islands of Walthard's cells. Almost always benign.

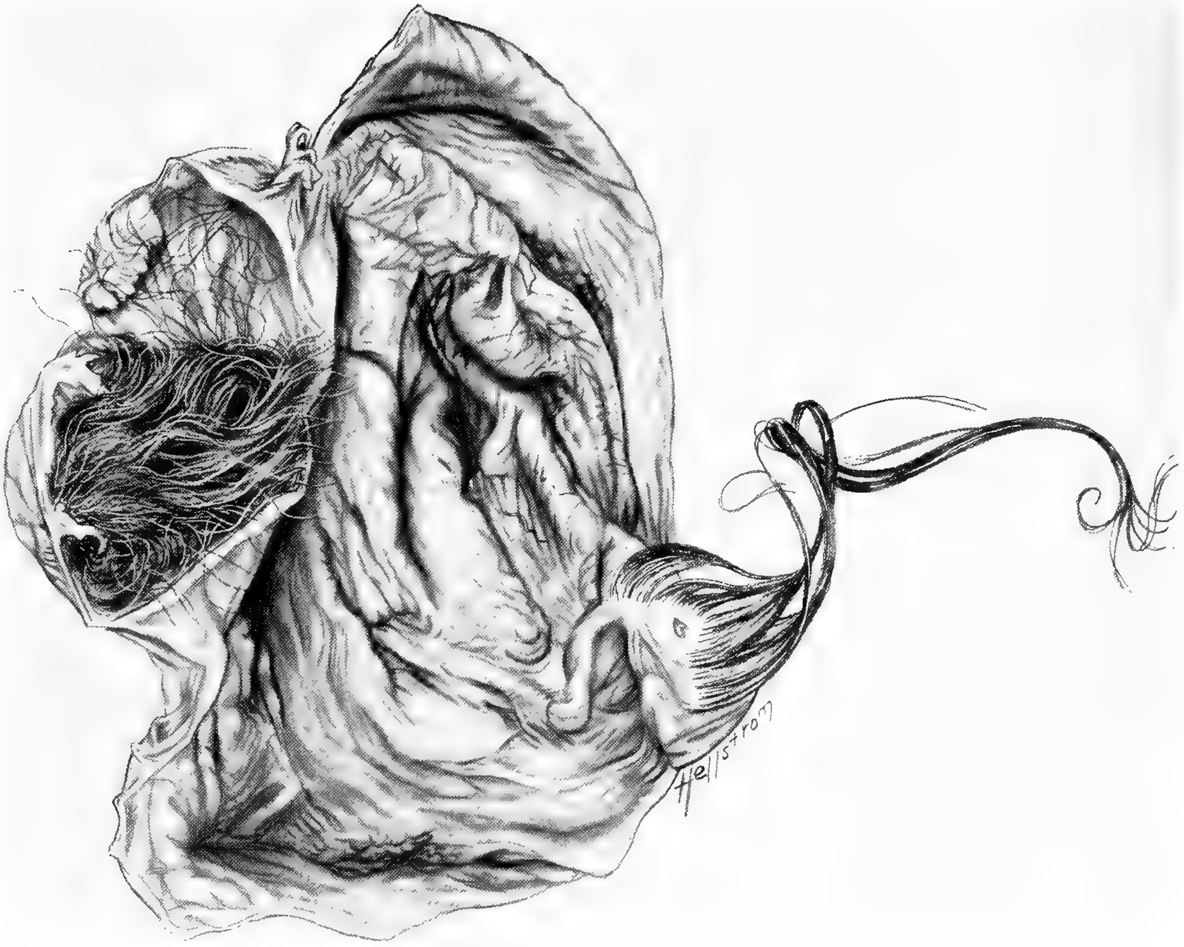


Fig. 249. Dermoid cyst of ovary. Lining has collapsed and greasy thick contents have been evacuated. Areas of long hair growth and one of calcification.

a more clear cytoplasm. These tumors are essentially never malignant, although a few that are malignant have been reported. The tumor acts like a fibroma of the ovary, may produce ascites, and the Meig's syndrome with hydrothorax, in addition to ascites. The tumor is slowly growing, may reach a large size, appears most frequently after the menopause, and has no hormone effect. The microscopic appearance of this fibroma-like tumor includes connective tissue cells with islands of squamous-like cells. Danforth and Arey reported a peculiar longitudinal grooving of nuclei of the latter. There also may appear a cystic degeneration of the centers of the groups of epithelial cells. Within the Brenner tumor, small islands of pseudomucinous epithelium may be found, and sometimes these areas of pseudomucinous epithelium form small cystic spaces which connect with the islands of Walthard cells. The pseudomucinous cyst possibly may have its origin in the Brenner tumor, as may the fibroma of the ovary. The idea that the Brenner tumor arises from the Walthard cell rest is interesting but strange, since more frequently the cell rests are found on the surface of the fallopian tube than in the ovary itself, and these tumors do not develop on the fallopian tube. Perhaps ovarian stroma surrounding these cells is

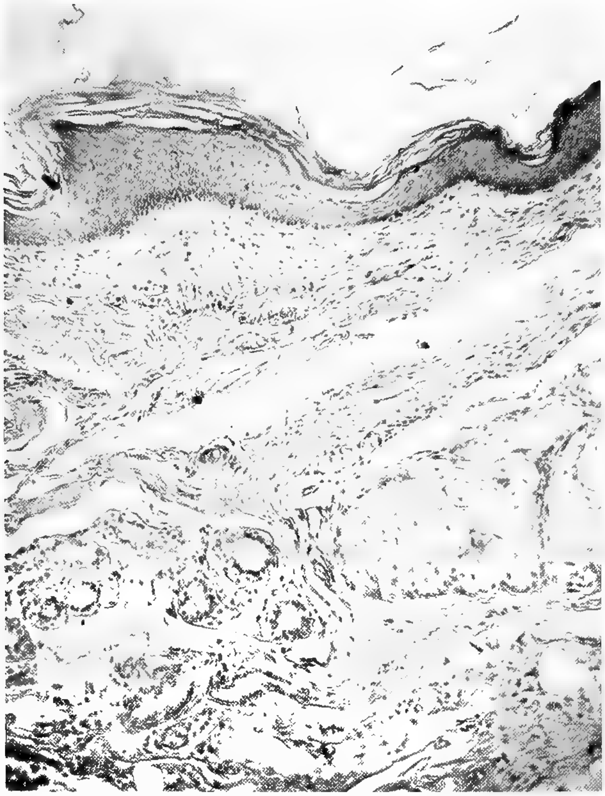


Fig. 250. Dermoid cyst of the ovary. The lining is that of skin with stratified squamous epithelium with some cornification. Within the wall are seen sweat glands and sebaceous glands.

required for the development of the Brenner tumor. Conservative excision of the tumor is indicated. The correct diagnosis can be made only by study of microscopic sections.

The *mesonephroma* is an unusual adenocarcinoma of somewhat papillary type, which Schiller described in 1939 as having a probable mesonephric origin. This is suggestive but not proven. The fact that within the tumor there are tufts of cells reminiscent of glomeruli and tubular patterns somewhat suggestive of the kidney, supports this delineation. The cells lining the tubules and about the imperfect glomeruli have a ragged pointed surface on the side of the cavity. Very few of these tumors have been reported.

The *dermoid cyst* is a form of teratoma, containing predominantly ectodermal elements, but also some mesodermal and some endodermal elements. This cyst is of embryologic origin, a form of twinning. It is the most frequently occurring abdominal tumor in the very young girl, and also is found throughout menstrual life, but rarely is found postmenopausally. The tumor clinically causes no symptoms except for some discomfort. On examination it commonly tends to press into the anterior cul-de-sac, that is, to gravitate in front of the uterus and over the bladder, and remain in this position, so that the uterus may be forced into retrodisplacement. When discovered, these tumors usually vary from the size of a lemon up to the size of a grapefruit, have a thick white wall, and are quite heavy. Their density must have some relation to their gravitation into the anterior cul-de-sac. They may become twisted, producing the symptoms of torsion of a pedicle and severe acute abdominal pain. Sometimes x-ray films of the abdomen reveal a tooth or other bony structure in the pelvis, which may indicate the presence of the dermoid cyst. The presence of any cyst of the ovary, of reasonable size, which persists longer than a period of six or eight weeks, indicates surgical excision. Usually there are mild or moderate symptoms of discomfort, although no menstrual abnormalities are associated. Operation reveals the soft, somewhat heavy, cystic tumor, which, when outside the abdomen, rapidly congeals to become firm and flattened on the surface against which it rests. When such a cyst is opened it contains thick oily material, usually much hair, and sometimes calcified areas. The microscopic appearance of the dermoid cyst is very characteristic. It is lined as a rule with squamous epithelium, with subepithelial hair follicles, sweat glands, and sebaceous glands. The latter are responsible for the material in the interior of the cyst. Within the cyst wall there may be cartilage or bone, and occasionally thyroid tissue, which are mesodermal in origin. Rarely intestinal epithelium may be present. Sometimes the squamous epithelium or other structures associated with the skin disappear, leaving a ragged lining. Foreign body giant cells and cholesterol crystals may be present in the wall. The presence of these may be diagnostic of the dermoid cyst, especially under some circumstances of infection and torsion. These tumors are said to be bilateral in ten per cent of cases, although this seems an excessive number. Five per cent are said to become malignant, and this seems high also. It would be our impression that a very much smaller per cent become malignant. The epidermoid carcinoma of the spinal cell type, and less commonly the sarcoma are the usual forms of malignant tumors arising in the dermoid cyst.

The *teratoma* is classified differently, a separate category from the dermoid cyst, though it is truly related. However, the teratoma contains three definite layers, ectodermal, mesodermal and endodermal, more equalized in distribution in the tumor. It is mainly a solid or partly cystic tumor, contains skin, brain, intestine, thyroid, in fact, any organ, and also undifferentiated areas of embryonic elements. It is from these undifferentiated areas particularly that embryonal carcinoma develops, and the majority of these tumors are malignant. It occurs more commonly in young individuals. Occasionally, within these tumors, an imperfect fetus may be thought to be present, as the tumor is considered a form of twinning. The teratoma is usually malignant, usually incurable, although undoubtedly some, if discovered early, may be cured by excision.

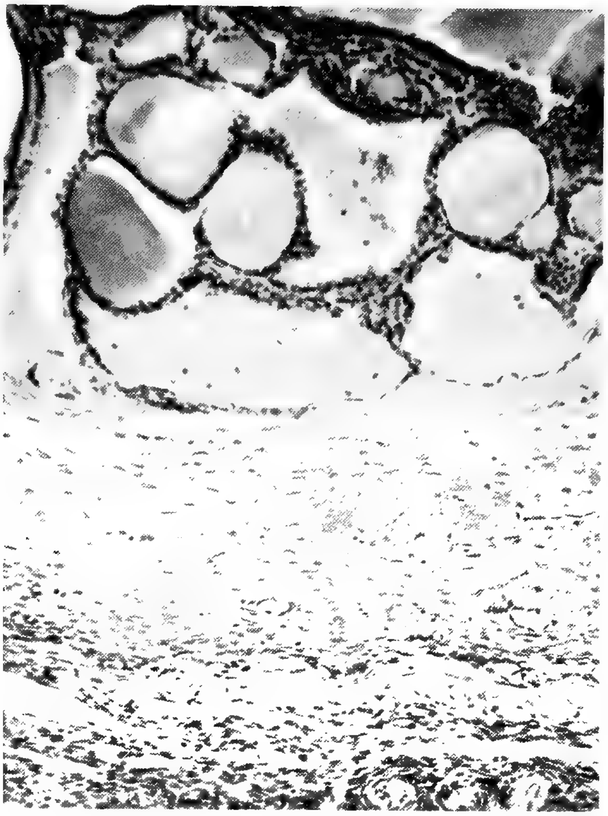


Fig. 251. Struma ovarii. The upper portion of the photograph shows typical thyroid tissue with colloid, without hyperplasia. A benign lesion. The inferior margin shows outside the capsule normal ovarian stroma. When all or the predominant portion of the teratoma is made up of thyroid tissue, it is called struma ovarii.

One form of the teratoma contains thyroid tissue as a prominent portion. Known as *struma ovarii,* these tumors may have no hormonal action, or they may become hyperplastic and produce hyperthyroidism. They may become malignant, metastasize to bone and be affected by radioactive iodine as the malignant tumors from the thyroid gland itself.

FIBROMA AND SARCOMA

The *fibroma* of the ovary is not too uncommon, occurs particularly in older women, more after the menopause, and may become quite large, though commonly it is six or eight centimeters in diameter. Minute fibromas of the ovary are so frequent as to be unimportant, and most of them never grow to become clinical tumors. The clinical tumors occasionally become large, fifteen or thirty or fifty pounds in weight, have a white surface, and may contain areas of hemorrhage and degeneration. These tumors may form ascites and hydrothorax, well known as *Meig's syndrome.* More often, the ascites is minimal, and hydrothorax absent or undiscovered. Apparently the ascites is due to the interference with the

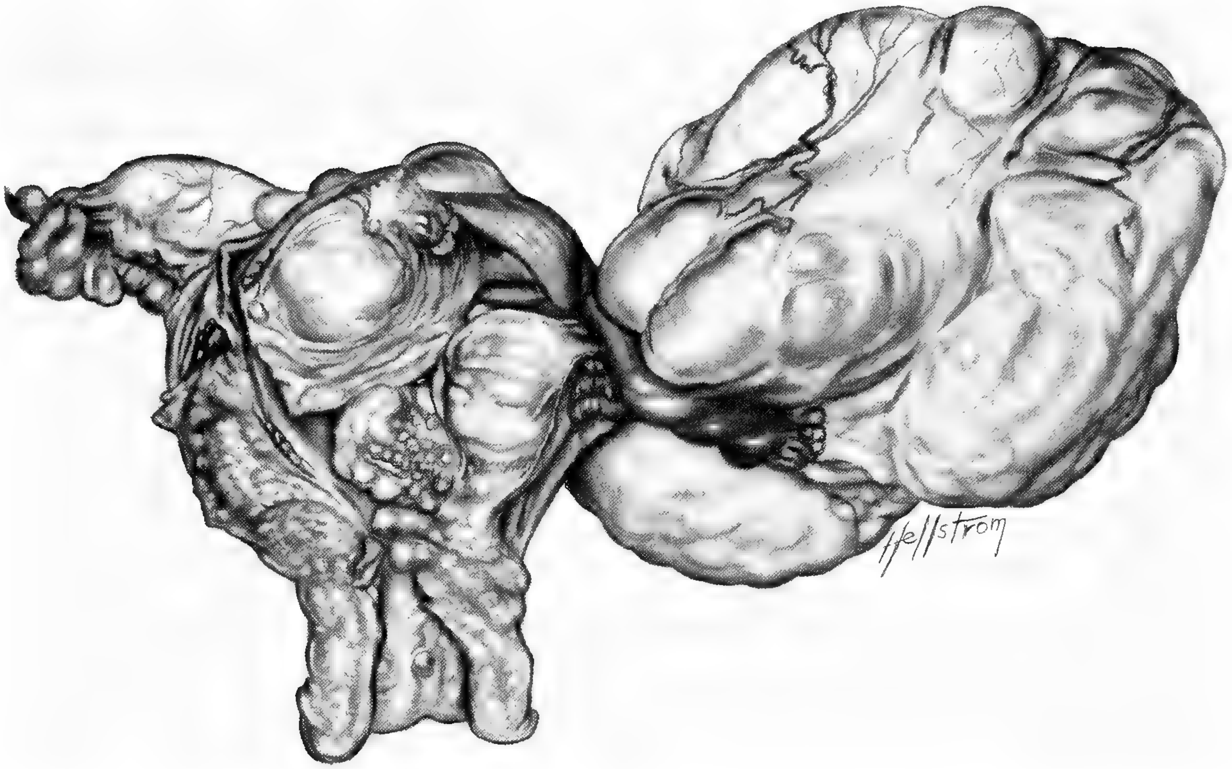


Fig. 252. Fibroma of ovary. Age fifty-six years. Pelvic discomfort. The possible malignancy from clinical examination proved to be a benign nodular fibroma. Also multiple myomas of the uterus. No ascites in this case.

venous return in the heavy tumor. The hydrothorax may be formed by the flow of the fluid through the lymphatics of the diaphragm into the pleural cavity, but this explanation is hardly enough to explain why hydrothorax does not occur with all other forms of ascites, as the same lymphatic channels must be present. It is true that hydrothorax may occur with other solid tumors. Torsion of the pedicle may occur with severe and acute abdominal pain. There is no hormone effect. Novak has stated that muscle bundles may be present, which means that these tumors may be fibromyomas. At times, areas of cartilage and bone are found. There is never any evidence of nuclear hyperactivity. Conservative excision is the usual treatment.

Sarcoma of the ovary is very rare, occurs mainly in the adult, and possibly arises in the fibroma. A spindle cell type is the more frequent type, the round cell less frequent. Excision is indicated when possible.

Lymphosarcoma is occasionally found in the ovary as an enlarged, firm, white nodular tumor, occurring at any age, but more often in the child. It is rarely cured by excision, because there are usually multiple points of origin, as in lymph nodes along the aorta. Occasionally the tumor may be radiosensitive, but usually only temporarily. Microscopically the tumor has a typical appearance of the lymphosarcoma, with a homogenous appearance of the round cells suggestive of the lymphocytic series. The newer forms of chemotherapy would be indicated as a trial, for residual or recurrent tumor.

GENERAL SYMPTOMATOLOGY AND DIAGNOSIS OF CARCINOMA OF THE OVARY

As with all of the ovarian tumors described in the section, an asymptomatic stage of growth, until considerable size has been obtained, and often extension and metastases of malignant cells, is the most prominent characteristic. Exceptions are the hormone secreting tumors, those producing estrogens or androgens, which cause obvious changes even when the tumor is relatively small. But these make up a very distinct minority of cases. Torsion, infarction and rupture may draw attention to the tumor as an emergency mechanical accident. The patient usually notices the abdomen is enlarging and thinks she is gaining excess weight. The physician finds ascites and a pelvic tumor mass. Pain is a late symptom, except with the acute emergencies, and follows compression from size of the tumor, invasion and metastases. Gastro-intestinal symptoms of nausea, cramping and constipation are not infrequent. Urinary frequency often occurs from pressure of the tumor. Abnormal menstrual bleeding, as metrorrhagia, prepubescent, or postmenopausal bleeding, in some degree occurs in fourteen per cent of the apparently non-hormone secreting serous cystadenocarcinomas. The explanation is not clear.

A complication of benign and malignant tumors is *torsion* of a pedicle. Since the former are more frequently occurring, torsion of this group is found more often. Included particularly are the pseudomucinous cysts, serous cysts and dermoid cysts. The cause of torsion is not clear. Perhaps intestinal motility or purely chance are related. The symptoms vary with the degree of trosion. When the pedicle is twisted two or three times, all of the blood supply may be interrupted and severe symptoms may ensue. Pain is very marked, degrees

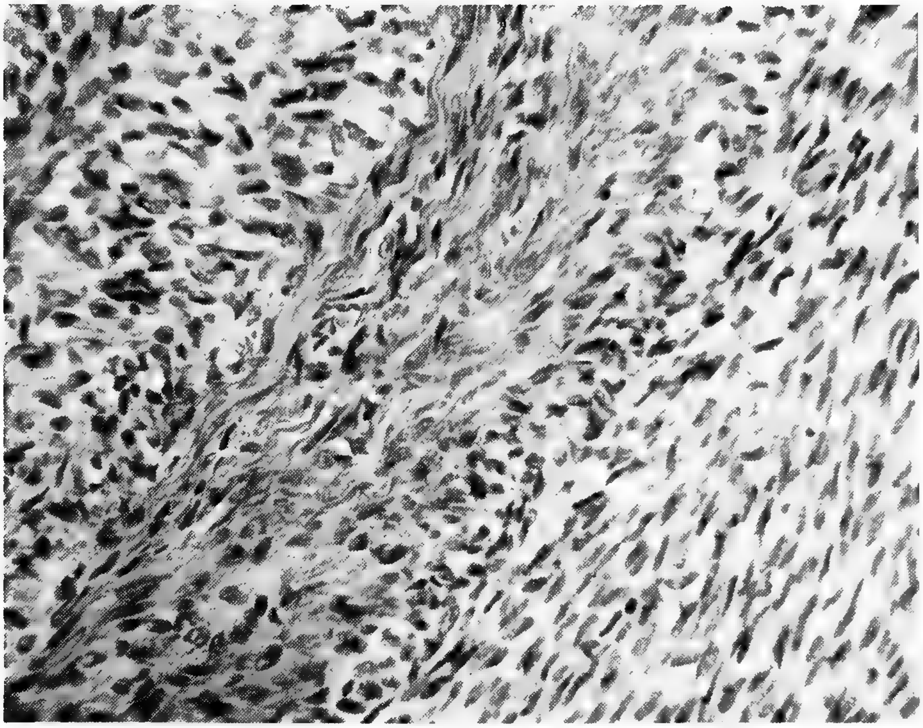


Fig. 253. Fibroma of the ovary. The broad strands of fibrous tissue seem extending in different layers in opposite directions. The nuclei are relatively regular.

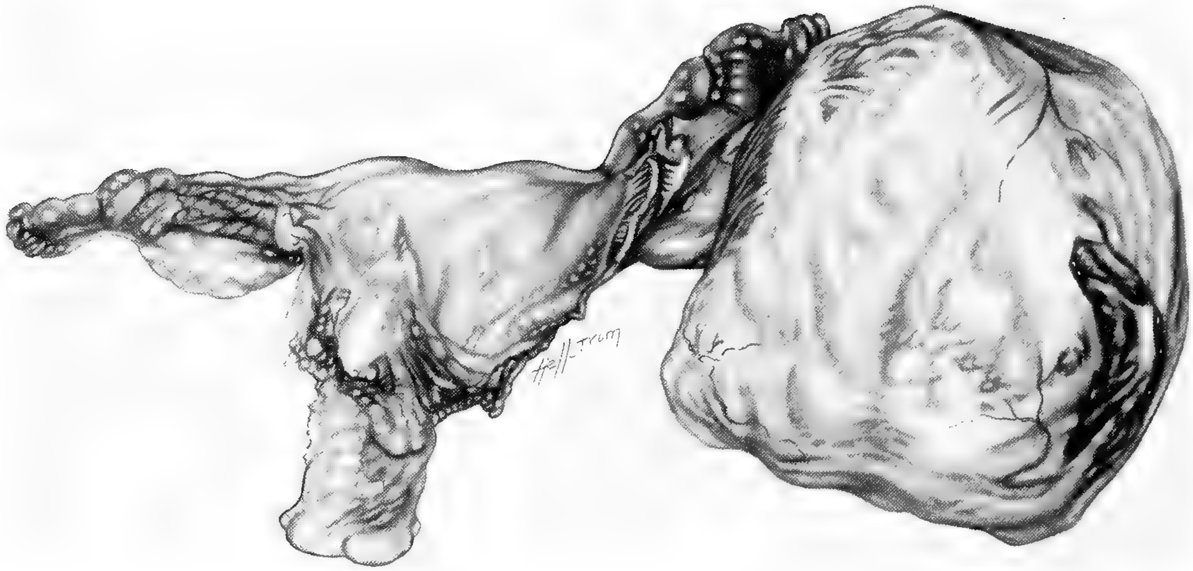


Fig. 254. Fibroma of ovary, benign. Age seventy-six years. Pelvic pain. The possibly malignant tumor proved to be benign. No ascites or hydrothorax in this case.

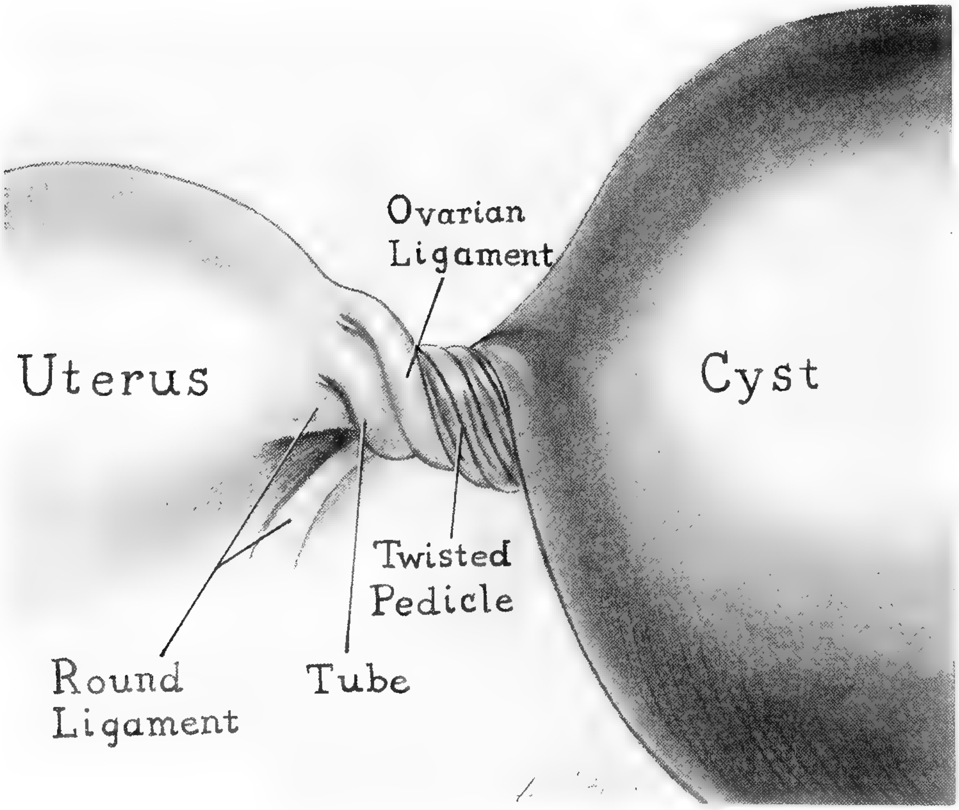


Fig. 255. Twisted pedicle. A triple twist of an ovarian cyst, involving the entire ovary, tube, and portion of the round ligament. The acute pain is severe. May cause shock. The twist may become untwisted or be partly reduced with improvement temporarily. This represents one of the acute abdominal emergencies in gynecology.

of shock are variable and the abdomen becomes extremely tender and rigid, with rebound tenderness. The tumor may be palpated on bimanual examination, but sometimes is impossible to feel because of the rigidity. The diagnosis of an acute surgical abdomen may be further clarified only by exploratory laparotomy. Acute salpingitis, ectopic pregnancy, acute appendicitis, volvulus, mesenteric thrombosis, intussusception, and acute pancreatitis may simulate torsion of the pedicle of an ovarian tumor. When the operation is delayed, rupture may follow. Chemical, followed by bacterial, peritonitis may be ex-

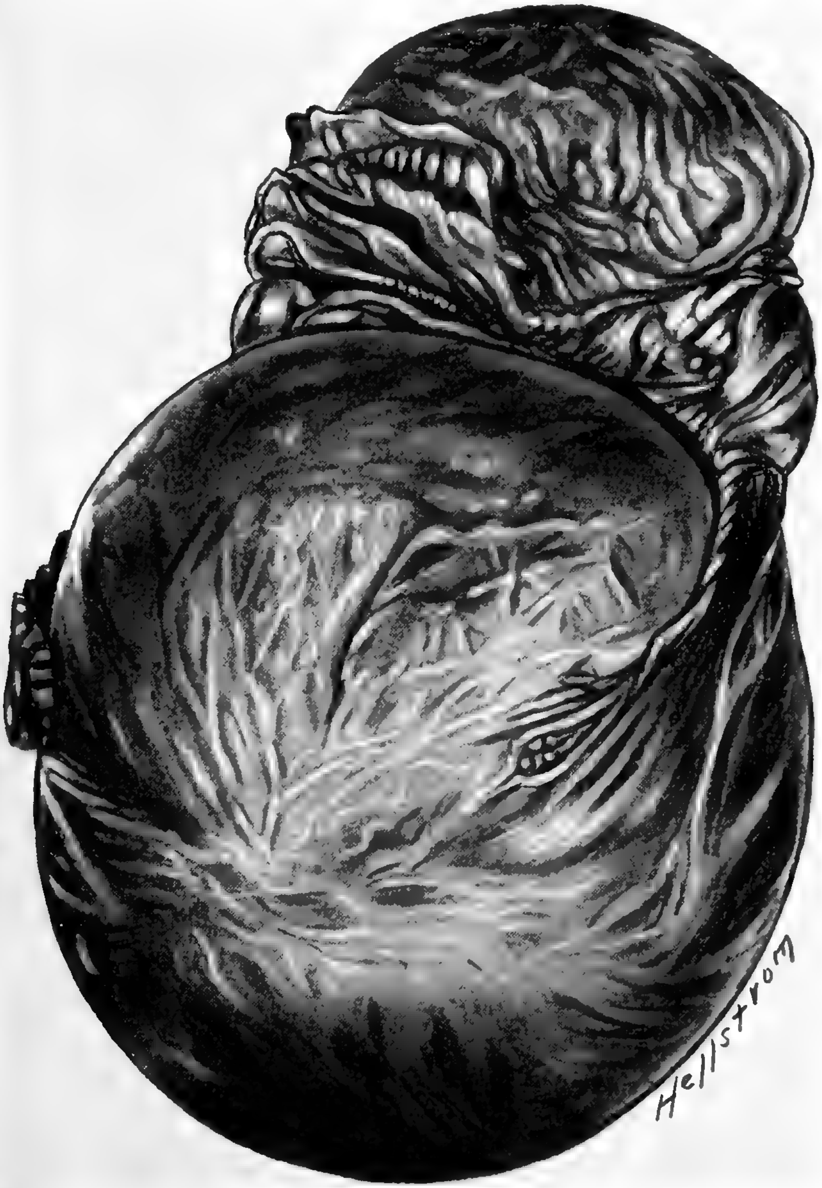


Fig. 256. Infarcted ovarian cyst due to twisted pedicle. The multilocular serous cyst has a black appearance, is filled with old blood clots, and the walls are partly necrotic.

pected. Extensive adhesions about the tumor may add some slight surface blood supply, but the illness may continue critical. The torsion may interfere only partially with the blood supply, and produce less severe symptoms. Or the torsion may be intermittent, apparently being reduced spontaneously and reforming, producing recurrent pain. Thrombosis of the ovarian veins distal to the torsion commonly occurs. During excision usually the pedicle is not untwisted for fear of dislodging a thrombus.

Rupture of a cystic tumor may occur spontaneously rarely, after trauma such as abdominal injury or sexual intercourse, or from pelvic examination. It is not infrequent that the corpus luteum cysts may be broken during examination, usually with no sequellae, but also the serous and pseudomucinous cysts may be ruptured similarly. This is serious when malignancy is present. Gentle examination is nearly always more revealing than a forceful one.

Differential diagnosis includes normal pregnancy, free fluid in the abdomen, pedunculated myomas to the side of the uterus, and a distended urinary bladder. The former is always to be suspected in differentiation of pelvic tumors: a careful history and attention to details in examination are most important, and pregnancy tests and x-ray films may be used as indicated. Free fluid causes dullness in the flanks and tympanny in the prominent portion of the abdomen from the free-floating intestines, whereas the large cyst produces dullness anteriorly and tympanny in the flanks. With carcinomatosis, free fluid is to be expected, and the original tumor if arising from the ovary may be most difficult to palpate. If there is obvious free fluid, tapping and study of the fluid for malignant cells may be helpful, while removal of the fluid may allow the tumor to be revealed. Pedunculated myomas may be impossible to differentiate from ovarian tumors, and exploratory operation should be performed in all when in doubt. The distended urinary bladder may confuse the expert. Catheterization and re-examination clarify the problem. The differentiation from tubo-ovarian inflammatory cysts, endometrial cysts, diverticulitis, abscess, omental and mesenteric cysts, and tumors of the bowel may be difficult. All are to be considered in accurate diagnosis. Tuberculous peritonitis may simulate carcinoma of the ovary with free fluid. In each instance there may be associated weight loss, mild local symptoms, doughy abdomen with fluid, and palpable infiltrating masses in the pelvis. Study of the fluid may be helpful, but exploratory operation usually is necessary.

CLINICAL CONSIDERATIONS OF CARCINOMA OF THE OVARY

Apparently one per cent of women's deaths after forty years occurs from carcinoma of the ovary. The over-all percentage of cure, after the lesion has been diagnosed, is fifteen to twenty-five per cent. The development of carcinoma of the ovary is extremely insidious. Sixteen per cent of cases have no symptoms of any kind, thirty-four per cent have only swelling, thirty-six per cent have pain, and fourteen per cent have vaginal bleeding.

This is mainly a disease of older women; sixty-three per cent occur after the menopause, and eighty-three per cent occur after the age of forty-three years.

The cancers grossly limited to the ovary have an excellent chance of cure after total hysterectomy and bilateral salpingo-oophorectomy, and do not need irradiation therapy (although cases with ruptured malignant cysts during operative removal generally are considered to need irradiation therapy). Patients having local extension in the pelvis may be cured in one-third of the cases by postoperative irradiation therapy, following total hysterectomy and bilateral salpingo-oophorectomy. With generalized carcinomatosis it is doubtful that irradiation therapy is of any curative value, although there may be prolongation of life in a small percentage with sensitive tumors. It is doubtful that radioactive gold is of any curative value, but ascites must be lessened in some cases. Nitrogen mustard and thiotepa (triethylenethiophosphoramide) not only may reduce ascitic fluid, but reduce the size of tumors temporarily. These drugs are toxic, and markedly depress the hemopoetic system. With careful administration they may prolong life a number of months. Numerous new drugs are being studied constantly in this field of chemotherapy.

Since there are no characteristic symptoms or tests for carcinoma of the ovary, only discovery of the tumors on routine pelvic examination offers any hope of early diagnosis after this lethal disease has started. Early diagnosis is difficult. There will continue to be errors and misdiagnosis of the malignant tumor or misinterpretation of the benign tumor, which cannot be avoided. Every woman should be urged to have examination of the breasts and pelvic organs every six months, and particular attention should be given to careful palpation of the ovaries on each occasion.

CHEMOTHERAPY OF CANCER

In gynecology, chemotherapy has seemed of greater importance in the treatment of ovarian carcinoma than in the other malignant tumors. While the results are somewhat more encouraging with ovarian carcinomas, chemotherapy is being applied to all gynecologic malignancies. Varying degrees of success and failure are being disclosed. Since extensive research is continuing in this field, which may at any moment bring dramatic results, a summary of this rapidly changing research is in order. C. P. Rhoads is credited with the organization and direction of much of the work in chemotherapy since World War II. Thousands of drugs have been, and are continuing to be screened, for antitumorigenic effects, as tested against mouse and rat tumors, including the standard sarcomas, carcinomas, ascitic cancers, and leukemias. Theoretical chemical syntheses are directed to blocking nuclear development and the metabolism of malignant cells. Large scale clinical testing of favorable compounds is proceeding across the nation. In addition to the private organizations, the National Cancer Institute has been allocated large funds for research in this field.

The major types of drugs that are being used in treatment today are (1) polyfunctional alkylating agents, (2) antimetabolites, (3) steroid hormones, and (4) miscellaneous agents (Karnofsky).

POLYFUNCTIONAL ALKYLATING AGENTS

Chemicals in this category are able to introduce alkyl groups into compounds of vital importance in the cell. These drugs differ in structure, solubility, and reactivity. There is evidence that desoxyribonucleic acid (DNA), the presumed genetic material of the nucleus, is most vulnerable to the introduction of the alkyl groups. This effect is not selective for neoplastic cells, though the latter do appear much more sensitive. Severe bone marrow depression is the most difficult complication from the uses of these drugs.

The alkylating compounds include methyl-bis (B-chlorethyl amine hydrochloride, HN_2, nitrogen mustard, mustargen). This agent, nitrogen mustard, has some chemical relation to sulphur mustard, the mustard gas of World War I. Since its introduction in 1946, it has had wide clinical use. Ovarian cancers, melanomas, lung cancers, and particularly leukemias, have shown some retarding of growth, for a few months, or a few years. Cure has not been obtained. This compound may be given intravenously, intramuscularly, intra-abdominally, intrapleurally, or otherwise. The leucocytes may diminish severely, anemia may develop, platelets may decrease, and purpura may develop. After a few days or few weeks, recovery from the bone marrow depression usually ensues, though a fatal outcome may intervene.

Other compounds include nitromin, chlorambucil, phenylanine mustard, triethylene melamine (TEM), triethylenephosphoramide (TEPA), triehylenethiophosphoramide (Thio-TEPA or TSPA), diepoxyspiperazine, and busulfan.

Triethelyenethiophosphoramide (TSPA) has been the most enthusiastically received in the treatment of hopeless carcinoma of the ovary. Bateman particularly has reported beneficial results, with regression of tumor, relief of ascites and hydrothorax, and prolongation of life for a few months to a few years. Other workers have had less encouraging results. This compound breaks down with heat, and in solution it is stable ten days or longer. The solution (10 mgm. per cubic centimeter) is sterilized by passing through a Seitz filter. Ten milligrams are given on alternate days for five doses, intravenously or intramuscularly, or larger amounts at one time may be given intraperitoneally, intrapleurally, or intratumorally. Blood examinations are repeated at intervals for three weeks, to determine leucopenia or anemia. The depressed white cells usually return to normal number after this time, when more TSPA may be given. The bone-marrow depression may persist for a much longer period of time. Otherwise the therapy may be continued or repeated at intervals, as indicated by the presence of the tumor.

Because of the severe bone-marrow depression, Creech and others have isolated areas of the body, particularly extremities, and perfused the tumor areas for short periods of time with high concentrations of the alkylating agents. The interrupted normal circulation is re-established after some minutes, or a few hours. This requires elaborate surgical procedures, and special pumps to circulate the chemically treated blood. Remarkable results have followed this experimental therapy, particularly with melanomas of the extremity treated with nitrogen mustard.

In conjunction with definitive surgery, particularly intra-abdominal surgery, Cole and others have perfused or irrigated the operative areas with solutions of alkylating agents as prophylaxis against the metastasis and re-implantation of tumor cells that may be present. These long term experiments are of great interest to observe.

ANTIMETABOLITES

These chemicals have quite variable structures, but are thought to interfere with metabolism of the cells by combining with enzymes to block their action, and to interfere with the synthesis of nucleic acids, preventing growth of many types of normal and neoplastic cells. The most prominent of these compounds being used today include amethopterin, aminopterin, azaserine, 6-mercaptopurine, and 5-fluoracil.

Aminopterin interferes with the conversion of folic acid to its formyl derivative, folinic acid, and thus blocks the availability of single carbon fragments for the synthesis of purines, pyrimidines, and amino acids (Karnofsky).

6-mercaptopurine interferes in the change of physiologic purines to form nucleic acid, and in the formation of co-enzymes. 5-fluoracil (Heidelberger, 1956) interferes with methylation of uracil, forming 5-methyluracil, and may prove an important new antitumorigenic agent.

STEROID HORMONES

The sex hormones may affect breast cancer to a remarkable degree (thirty-five or forty per cent seem hormone dependent). Apparently the estrogen does not cause the carcinoma to begin, but certainly its growth may be greatly enhanced by the presence of estrogen. In women younger than five years after the menopause, the presence of metastasis is an indication for bilateral oophorectomy, (statistics indicate that irradiation castration is not as satisfactory). As not all the estrogen may be removed by oophorectomy, bilateral adrenalectomy may be performed. Of late, cortisone therapy has seemed to depress the adrenal gland sufficiently to obviate this operation. Hypophysectomy has been advocated to alleviate metastases for this and other forms of malignant tumors (Ray), thus removing gonadotrophic and adrenotrophic hormones, and removing the general growth hormone.

Androgens, in several different forms, have been used with some success in younger women. The mechanism probably is by interfering or neturalizing the estrogen present. A large amount of androgen is necessary to neutralize a normal amount of estrogen. The virilism that necessarily follows is most annoying.

Strangely, in elderly women with carcinoma of the breast and metastases, estrogens may cause regression of the cancer to a remarkable degree. This opposite effect is not understood.

Cortisone and related compounds cause regression of lymphatic tissue and inhibition of growth of certain mesenchymal tissues. While this is a direct anti-tumorigenic effect in certain tumors, it appears that part of the action in the case of carcinoma of the breast may be inhibition of the adrenocortical estrogen. Prednisone has been the most widely used adrenal steroid in neoplastic disease.

There is no evidence that carcinoma of the cervix is affected by hormone therapy, whether estrogenic, androgenic or adrenocortical. Nor is there any evidence that endometrial carcinoma and ovarian carcinomas have any direction relation to these hormones, although one tends not to give estrogens after the latter are discovered.

MISCELLANEOUS COMPOUNDS

In a group that are not as well understood or classifiable in chemotherapy for cancer are included urothane, which depresses certain tumors, as the myeloma, colchicine which interferes with mitosis and produces metaphase arrest, and the actinomycins. The latter are highly toxic antibiotics, but also depress certain malignant tumors.

APPLICATION OF CHEMOTHERAPY FOR CANCER

Early diagnosis and early excision comprise the best treatment for cancer. When there is spread of the tumor, irradiation therapy alone may be indicated. A combination of surgery and irradiation therapy often makes the best approach.

Chemotherapy in most instances remains an experimental tool. In the leukemias or widely metastatic diseases no other therapy may be available. As a rule the standard methods must not be discounted too soon for a new approach.

It does appear that chemotherapy offers hope of more and more arrests, prolongation of life, comfort, and even cure of disease. In acute leukemia of children, there has been complete remission for a few months after use of antimetabolites and adrenal steroids. Unfortunately, the disease soon becomes resistant to all forms of treatment. Chronic myeloid leukemias have not been relieved by chemotherapy. Alkylating agents and adrenal steroids may produce remissions with chronic lymphoid leukemia. Similar treatment has been helpful in Hodgkin's disease. The life and comfort of the patient with breast carcinoma may be materially aided by proper hormone therapy in the individual case, and occasionally the alkylating agents cause regression. Choriocarcinoma has been strikingly benefited by nitrogen mustard and thio-tepa in several patients. Prostatic cancer has had remissions after castration and administration of estrogen, a standard therapy of today. Lung cancer has shown temporary relief after nitrogen mustard therapy in one-third or one-half of the cases. Ovarian cancer has shown objective regression and symptomatic relief after nitrogen mustard, TEM, and TSPA in a varying percentage of cases. Wilm's tumor and rhabydomyosarcoma have been temporarily benefited by actinomycin D. Practically all of the tumors become resistant to drug therapy after varying periods of time and many of the major forms of cancer, including carcinomas of the cervix and endometrium, do not show any consistent benefit from chemotherapy. This is a difficult field of research requiring painstaking study by the chemist, the biologist, and the clinician.

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CHAPTER X

Endometriosis

Endometriosis is a pathological condition characterized by the presence of endometrium in an abnormal location. As a rule, this term is used to mean external endometriosis, or the presence of endometrium outside of the uterus, whether it be in the fallopian tube, or the ovaries, or the pelvic peritoneum, or the wall of the bowel, or in extragenital locations. However, in addition to this large and extremely important form of endometriosis, with its great variations in extension and location, known as external endometriosis, there is also to be considered internal endometriosis, or adenomyosis of the uterus. Some have considered that this is an entirely separate form of disease, and has no relation to external endometriosis. Actually, the external form probably makes up about sixty-five per cent of all cases of endometriosis. The internal form, or adenomyosis, makes up about twenty-five per cent of cases; and a combination of the two occur in ten per cent or fifteen per cent of cases. This combination of adenomyosis of the uterus and endometriosis outside the uterus does seem to have a connection, when it is found; or, at least, the association is more frequent than chance alone. Actually, external endometriosis is associated with many other forms of pathology, especially after the age of thirty-five years. The association of myomas of the uterus, for instance, so frequent in later menstrual life, is definitely more frequent than in women in general. At any rate, these forms will be discussed in this chapter under the single heading of pelvic endometriosis.

Rokitansky, in 1860, first described adenomyosis of the uterus, or the presence of endometrial glands in the myometrium of the uterus. von Recklinghausen, from 1885 until 1900 or so, was extremely interested in this disease, and felt that the endometrial glands were separate from the endometrium, and that they probably represented remnants from the wolffian ducts. From 1895 on, Thomas S. Cullen became especially interested in this disease, prepared a number of publications, and even published a book on the subject, *Adenomyoma of the Uterus*. Cullen made serial sections personally of many uteri with adenomyosis, and showed that the basalis of the endometrium in the cavity of the uterus always connected with the glands and the stroma that were down in the wall of the uterus, showing that it positively was mullerian in origin and that the growth in the wall extended from the endometrium itself. He even showed the extension of this endometrium completely through the wall of the uterus into the cul-de-sac and into the wall of the rectosigmoid, operating on a number of such cases, and obtaining beautiful specimens with advanced disease. At that time, Cullen thought that all endometriosis in the cul-de-sac, which formed thickening and which he called adenomyomas of the rectovaginal septum, probably always came from this extension through the wall of the uterus. In later years, we are to learn that, while this may be possible in rare instances, as a rule the endometriosis in the cul-de-sac is separate, and represents external endometriosis, associated with a growth on the peritoneal surfaces. In 1899, Russell reported a single case with mullerian duct remnants in the ovary. Apparently this was the first reported case of endometriosis of the ovary, although he did not use this term. Sampson in 1921 and 1922, published two papers of extraordinary interest. The first was entitled,

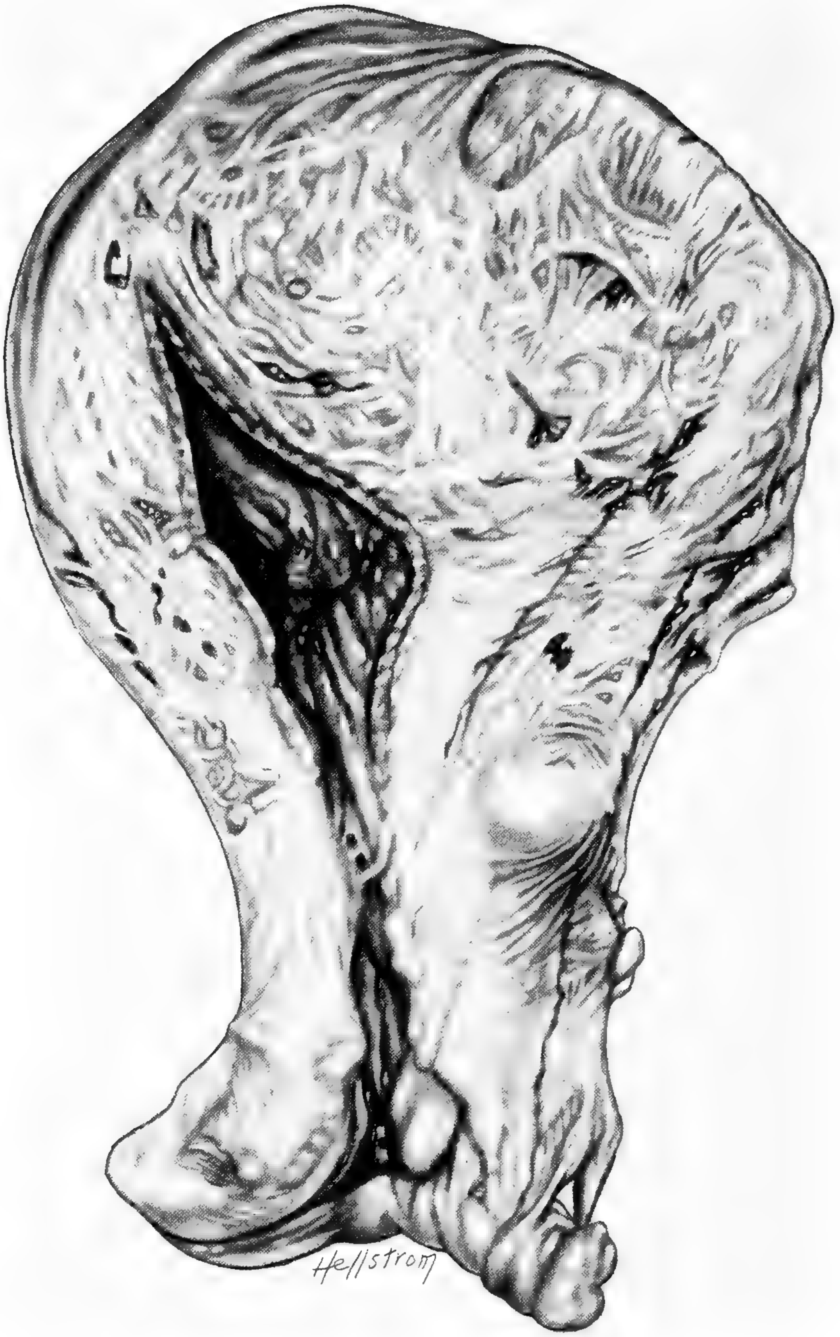


Fig. 257. Adenomyosis of uterus. The quite coarse-grained scarring in the thickened wall is characteristic. Here, the change is more marked in the posterior wall. Small dark areas represent collections of old blood within the islands of endometrium. The polypoid endometrial hyperplasia is frequently associated, as are myomas of the uterus. This specimen also has an endocervical polyp and lacerations of the cervix.

"Perforating, Hemorrhagic, Chocolate Cysts of the Ovary," and in the second he spoke of "endometrial cysts of the ovary," apparently using this term for the first time. These two original papers were most thorough and careful in their delineation of the disease of external endometriosis as we know it today, and very little has been added to the pathology or understanding of the disease, as far as basic concepts are concerned. Sampson believed that the most likely explanation of the origin of endometriosis was by retrograde menstruation from the cast-off endometrium at the time of menstruation, fragments passing back through the fallopian tubes and into the peritoneal cavity. The distribution of the implants of endometriosis on the ovary, behind the uterus in the depth of the cul-de-sac, and over the uterosacral ligaments, may be logically explained by the implantation of endometrial fragments in menstrual blood in a woman in the erect position, since they would seem to be carried by gravity into this dependent area. At the same time, Sampson did mention the possibilities elaborated on so much since that time, that the endometrial implants may have arisen from congenital remnants of mullerian duct cells, and in some instances from lymphatic metastasis, or blood stream metastasis. During the next thirty years, Sampson was to publish many more papers on the subject of endometriosis, adding further details to our knowledge of today; but his two original papers are classics and represent one of the very great contributions to gynecology. Since Sampson's original work, several hundred papers and articles have appeared on the subject of external endometriosis, some including large series of five hundred or more cases, with elucidation of symptoms, diagnosis and treatment. Much interest has developed over experimental production of endometriosis, particularly since the paper by TeLinde and Scott in 1950, in which external endometriosis in the peritoneal cavity was produced in the macaque monkey by transecting the cervix and diverting menstrual blood into the abdominal cavity. TeLinde and Scott, both in this paper and in subsequent papers, feel that they have proved the implantation of desquamated menstrual epithelium into the peritoneum of these monkeys. On the other hand, Allen, Peterson, and Campbell, from their studies of monkeys are somewhat doubtful of the true implantation of desquamated epithelium, and raise the question again that the menstrual blood may act as an irritant to the pelvic peritoneum and cause changes in embryonic remnants in this area.

The origin of endometriosis in different situations may have several possible explanations. The wolffian duct theory of von Recklinghausen has not been thought of again in relation to endometriosis since Cullen disproved the origin of adenomyosis of the uterus in this manner. Russell's suggestion of mullerian duct remnants remains today as a theory of the congenital origin of endometriosis. In 1925, Ivanoff, of Russia, presented his thesis of the serosal theory of the origin of endometriosis. His idea was quoted and popularized by Robert Meyer, of Germany, who believed with him that endometrial implants arose from undifferentiated cells of the celomic cavity, cells which remain in the peritoneal cavity in the adult, which were related to those cells later to form the mullerian duct system, and which have the potentiality to develop into an adult form of genital tissue. Just why it should always take the form of endometrium, and not many other forms of pelvic organs, is not explainable. The Ivanoff-Meyer theory supposed that the serosal cells with adult endometrial potentialities might be stimulated by irritation from inflammation. Later advocates have felt that retrograde menstrual blood might have the irritating effects that could cause these potential serosal cells to develop into endometrium. The explanation of endometriosis in the bracheo-radialis muscle of the forearm reported by Navratil and Kramer in 1936, and of endometriosis in the thigh, reported by

Schlicke in 1944, and the report of endometriosis in the kidney by Marshall in 1943, and the three or four reports of endometrium in the pleura and lungs, in the past three or four years, have been explained by the serosal theorists that the remains of some of the celomic epithelium may even be present in the limb buds of the upper or lower extremities, where the celomic cavity originally extended in embryonic life, and similarly in the pleural cavity which was closely associated with the celomic cavity. The theory of retrograde menstruation through the fallopian tube, as originally advanced by Sampson, continues to have many advocates, and particularly after the experimental work of TeLinde and Scott on their monkeys. The occurrence of a small cervical os, the frequent association of retrodisplacement of the uterus, the finding of retrograde menstruation at intervals in women who are operated on during menstruation, the distribution of implants in the peritoneal cavity in its most dependent portion, seem logical as an explanation for external endometriosis in the majority of instances. That there must be other explanations for extrapelvic lesions is obvious.

The lymphatic theory was advanced by Halban in 1925, who felt that most instances of endometriosis might be explained by lymphatic metastasis. While endometriosis has been reported in inguinal lymph nodes in a very few cases, which obviously is lymphatic metastasis, this theory has been largely discounted. Recently, Javert has reported some five cases with endometrial glands in pelvic lymph nodes, discovered in his pelvic lymphadenectomy operations. Endometriosis of the umbilicus does occur without the presence of external endometriosis in the peritoneal cavity. While some have suggested that endometrial implants may be swept into a minute hernial sac in the umbilicus, there should almost always be other implants of endometriosis in the pelvis if this were true. As some of the lymphatics from the pelvic organs do travel up along the undersurface of the abdominal wall to the umbilicus, as demonstrated by injection techniques (Scott), it is certainly plausible that umbilical endometriosis may follow lymphatic metastasis, unless it is of congenital developmental origin.

Metastasis by way of the blood stream has always remained a possibility for the development of endometriosis. It hardly seems logical that endometrial implants would circle by way of the blood circulation and implant in the cul-de-sac of Douglas. On the other hand the occurrence of endometriosis of extragenital origin may well be related to blood stream metastasis. This includes the endometriosis in the lung, in the forearm, and in the thigh. But, certainly these have been most rare cases. Meigs believes that endometriosis may begin in young people, because of the uninterrupted menstrual cycles which allow the bombardment of the peritoneal serosal epithelium with cyclic hormones to produce endometriosis. Novak had supported the serosal theory of Ivanoff and Meyer, and believed that the serosa may be stimulated to become endometriosis, particularly by hormones. Meigs has elaborated on this and believes that the uninterrupted cyclic stimulation by hormones in regular menstrual cycles may affect the serosal cells, which have the potentiality of developing into mullerian epithelium. Early and frequent pregnancies, according to his theory, are of value to prevent the development of endometriosis, by stopping this cyclic stimulation for nine months at a time. Javert (1949) has suggested that we accept a comprehensive theory, and do not hesitate to use all of these different suggestions as the possible origin of the individual case with endometriosis, a viewpoint that most gynecologists probably have accepted for some time. Perhaps someone will prove a universal origin of all cases of endometriosis, which actually may be quite different from our present views.

ADENOMYOSIS

In internal endometriosis, or adenomyosis of the uterus, the basalis of the endometrium turns and invades the myometrium of the uterus, the stroma proceding ahead and carrying with it the basal glands of the endometrium. These extensions proceed between the muscle bundles in a very tortuous and irregular manner, and can be followed only by serial sections to prove that they are connected. Most often the extension is only to a small degree in the myometrium; probably a slight extension into the myometrium is normal. But, extension one-third of the depth of the myometrium, is a quite frequent occurrence, especially in the uteri of women after thirty-five years of age. Extension of the endometrium much deeper, as to the serosa of the uterus, occurs less often. Rarely, it has perforated the serosa of the uterus. As a rule, the endometrium of adenomyosis does not show secretory or progesteronal effects in the luteal phase of the cycle, this basalis of endometrium being relatively insensitive to progesterone. In a small percentage of cases with adenomyosis the invading areas do show secretory change. It may form a premenstrual, glycogen-containing, sawtooth type of endometrium. During pregnancy, with the extremely large amount of progesterone and estrogen present, the adenomyosis regularly develops the decidual appearance.

Endometrial hyperplasia and anovulatory

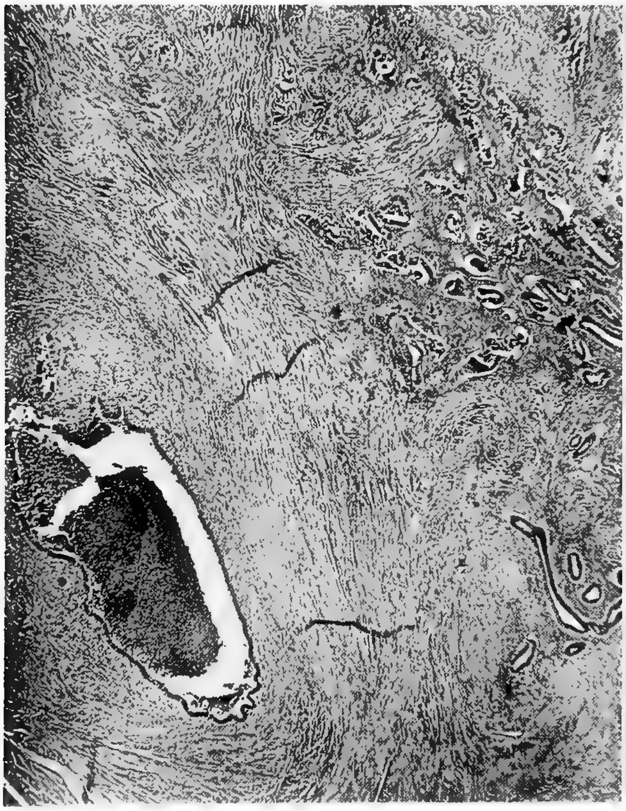


Fig. 258. Adenomyosis of uterus, low power. There are multiple areas of endometrium through the myometrium. In the right upper quadrant there is much endometrial stroma about the multiple glands. In the left lower quadrant there is a dilated endometrial cyst containing old blood evidently due to bleeding within itself during menstruation.

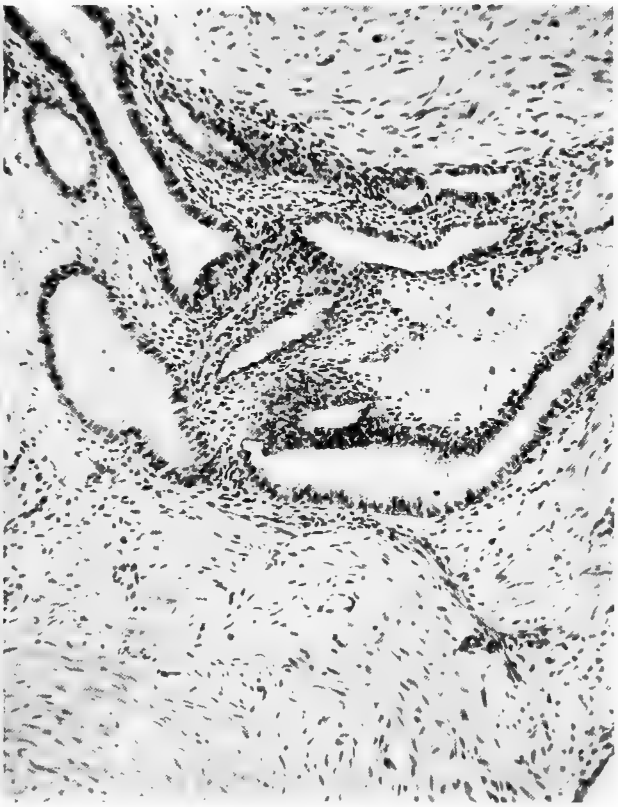


Fig. 259. Adenomyosis of uterus, medium power. The endometrial glands show non-secretory effect, particularly demonstrated because the lining cells are piled up two, three and four layers thick, which does not occur in the secretory state. The nuclei are rather hyperplastic. There is a slight amount of surrounding stroma showing some mitoses.

endometrium in the last half of the cycle are definitely more frequent in cases with adenomyosis than normal. This was shown by one of the author's students, Spatt, in 1946. It was also mentioned, though in a somewhat lesser percentage, by Novak and de Lima in 1948. Novak further states that the basalis itself, in many cases of adenomyosis, shows an unusual degree of hyperplasia of a nonsecretory epithelium with increased cystic dilatation of glands. The absence of ovulation in greater incidence than normal and increased hyperplasia do suggest that increased secretion of estrogenic hormone and the absence of progesterone may be factors in the development of this disease.

Adenomyosis may surround the endometrial cavity and cause enlargement of the wall to one and a half to three or four times normal thickness, with great increase of fibrosis in the wall of the myometrium, which appears grossly as thickened interlacing bands of scar tissue. Within these bands there may be seen minute areas of old hemorrhage. In a certain percentage of cases, the anterior wall of the uterus is much thickened over the posterior wall, so that examination of the patient may suggest that the uterus contains an intramural myoma in the front wall, or possibly a submucous myoma. Immediately preceding menstruation, the uterus always enlarges, though the degree may be quite variable. This is especially true with adenomyosis, and at the time of menstruation areas of minute bleeding may occur in the adenomyosis itself. In fact, commonly there is, but apparently not always is there this bleeding. Certainly the bleeding is not marked, and is hardly enough to cause a degree of pain that is related to the dysmenorrhea of adenomyosis.

Adenomyoma has been used as an interchangeable term with adenomyosis, but really should be reserved for the very rare instance of the encapsulated tumor, perhaps of a myoma itself containing endometrial glands, or an encapsulated, rounded tumor of adenomyosis. The latter conditions are quite un-

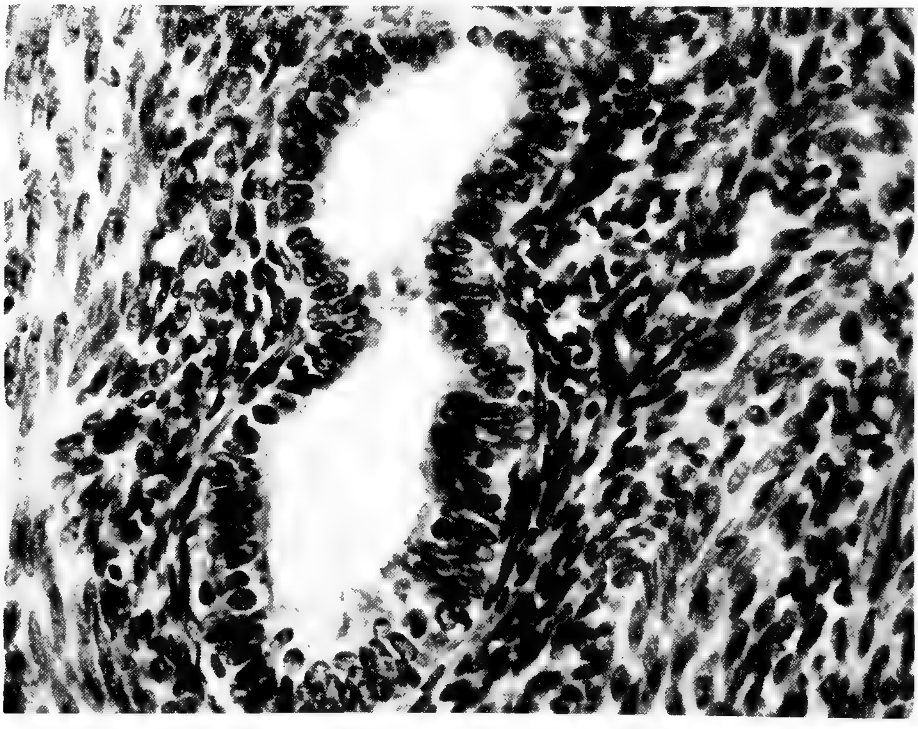


Fig. 260. Adenomyosis of uterus, high power. The lining epithelial cells are non-secretory, show some piling-up, and resemble tubal epithelium. The surrounding endometrial stroma is typical.

common, since, as a rule, there is no distinct and separate tumor but a more diffuse enlargement. As a rule, the term adenomyosis is preferable. These terms similarly are used when nodules are found in the rectovaginal septum, or in the wall of the intestine. In these instances, the endometrial glands are surrounded by fibrous tissue stroma, and apparently by some smooth muscle, so that the muscle is carried in or does develop from the stroma about the glands. These terms may continue to be used, but the tendency is to speak of these lesions as endometriosis of the bowel and rectovaginal septum.

SYMPTOMS

The patient with adenomyosis of the uterus may have no symptoms, but more characteristically she complains of severe dysmenorrhea and menorrhagia. The cause of the dysmenorrhea is certainly not clear. One would suppose that bleeding into the islands of endometrium down in the myometrium may explain the pain, and perhaps it does, though the bleeding is never very extensive. Certainly one would doubt that progesterone is a cause of symptoms here, as it must be in the functional dysmenorrhea in young women, particularly because endometrial hyperplasia and anovulatory endometrium are so frequently associated with this disease. The menorrhagia may be related to the hormonal changes which cause anovulatory endometrium and hyperplasia, but equally it may be explained by the abnormality in the myometrium, which may interfere with its contractility and its control of blood flow. Often, the patient with adenomyosis has intermenstrual pelvic pain, bearing-down, pressure discomfort, a heaviness in the pelvis, associated with first degree descensus, retrodisplacement, cervicitis, and relaxations with cystocele and rectocele. This disease seems to develop much later in menstrual life than does external endometriosis, as shown by the fact that the vast majority are operated on at ages forty to forty-five, certainly well after the age of thirty-five, and second by the fact that the majority of these patients have had children in younger life. Only five per cent of patients with adenomyosis of the uterus have complained of sterility in their younger years. Apparently with the anovulation and endometrial hyperplasia, the disease does develop in later years.

DIAGNOSIS AND TREATMENT

A diagnosis of adenomyosis is made with no degree of accuracy, and often it remains as a possibility. When there are symptoms of menorrhagia and dysmenorrhea that are acquired in late menstrual life, with degrees of enlargement of the uterus, especially asymmetrical enlargement of the anterior or posterior walls, one may suspect adenomyosis. Often the excised uterus shows only a fibrosis of the uterus, or subinvolution, or perhaps an intramural or submucous myoma.

The treatment of adenomyosis of the uterus is hysterectomy if the symptoms are sufficiently severe. This lesion is never a premalignant one; and while any tissue may change into malignancy, this disease is noted for its benignity, and only incapacitating or serious symptoms merit surgical excision. Conservation of the ovaries is indicated, particularly before the menopause, provided there is no endometriosis in the ovaries or other serious ovarian pathology.

Stromatosis and stromal myosis are terms that are used to represent a growth of stroma-like tissue through the myometrium, which characteristically invades the lymphatics and may extend outside the uterus into the broad ligaments. This acts as a malignant tumor, is cured only by extensive excision, and in some instances may metastasize. That this represents a form of endometriosis is very problematical, and this disease is discussed in further detail under Diseases of the Myometrium.

Salpingitis isthmica nodosa has been mentioned under Diseases of the Fallopian Tubes. In this strange disease, the isthmus of the fallopian tube in the cornual areas of the uterus, becomes enlarged, thickened, pipestemmed, usually one or two centimeters in diameter for a distance of two or three centimeters, after which the fallopian tube reverts to complete normality out through the fimbria. This marked hard thickening and enlargement of the wall of the tube has been thought by many to represent a form of inflammation. Sections of this tube, however, show islands of endometrium in markedly thickened tubal and cornual muscle, so that the appearance is entirely that of adenomyosis. There may be no other adenomyosis in the uterus itself, in fact, usually there is not. This disease causes sterility by closing the tubal lumina and may be associated with no other pathology in the pelvis. Its cause is unknown. If it can be diagnosed in the patient with sterility, dymenorrhea, and some pelvic pain, with some palpable enlargement of the uterine cornua, and confirmed to some degree by a hysterogram showing complete absence of tubal patency, exploration may reveal salpingitis isthmica nodosa. It may be treated by excision of the cornual portion of the tube and reimplantation of the tube into the endometrial cavity, using a polyethylene tube as a splint. The splint is sutured into the cervix and left in place for ten days.

EXTERNAL ENDOMETRIOSIS: PATHOLOGY

The distribution of endometrial implants in external endometriosis is essentially limited to the lower portion of the abdomen below the level of the umbilicus. This strange essential limitation must have some important connotation. While the implants may occur on the ovary, on the surface of the uterus, on the pelvic peritoneum, the wall of the colon and terminal ileum, they are never present above the level of the connection of the lower ileum to the umbilicus in fetal life — that is, above three feet from the iliocecal valve where the Meckel's diverticulum would be placed, if such were present. Implants are always below this level. Also, while endometriosis may occur in the umbilicus, it does not occur above it. This is essentially true, though there have been a few exceptions. The most frequent occurrence of endometrial implants is in the posterior cul-de-sac. Here, minute brownish, puckered, granular areas of a few millimeters in diameter, or minute purple cysts surrounded by some scarring and greyish or brown discoloration, are found in the center of the cul-de-sac, where the rectum joins the vagina. Even more frequently these implants are found on one or both uterosacral ligaments. These small thickened areas are produced by a reaction surrounding the endometrium itself of rather marked degree, so that the areas are quite firm, especially seeming so to palpation from examination through the vagina and rectum. Adhesions of extremely dense character between the rectum and the back of the cervix and back of the uterus are quite frequent. They have a thick and tough character, are separated with great difficulty and usually require sharp dissection with the scissors or scalpel. These dense adhesions are associated with adjacent thickening in the serosa of the cervix and uterus, and even more definite thickening in the muscularis of the bowel where these areas are adherent. These peculiar adhesions are most characteristic, and may have a few scattered areas of recognizable endometriosis within them. Next in frequency of distribution of endometrial implants is the ovary. There may be only minute surface implants of one, two or four millimeters across in multiple areas on the surface of the ovary, brownish and granular; some have minute purplish cysts in the

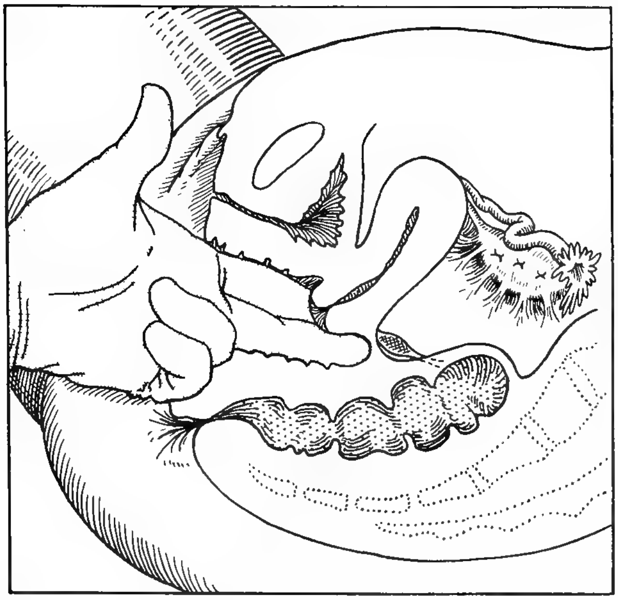


Fig. 261. Early external endometriosis (diagram). Implants on the ovary menstruate and cause dense adhesions, particularly to the undersurface of the broad ligament. The shotty thickening in the utero-sacral ligament is diagnostic.

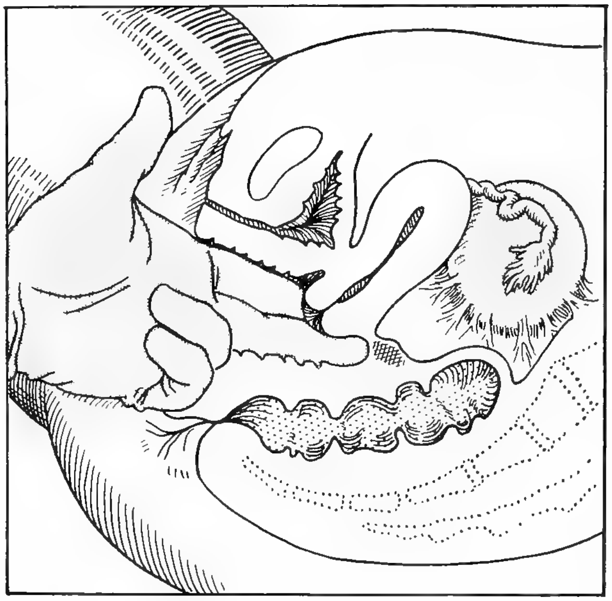


Fig. 262. Endometrial cyst (diagram). This cyst is almost invariably adherent, caused by minute perforations, which are extremely irritating to the adjacent peritoneum. The diagnosis is distinguished from the tubo-ovarian inflammatory cyst and the malignant cyst by the presence of typical shotty nodules in the cul-de-sac.

centers of these implants. There may be puckered areas with constriction of the surface of the ovary, which is retracted by the fibrosis of scar tissue surrounding the area of implantation. These little puckered scars are characteristic, as they are in the pelvic peritoneum. Endometrial cysts, or chocolate cysts, are most frequent in the ovary; the endometrium burrows within, and the surface becomes sealed over. With repeated menstruation within the contained area, there may develop the increasing volume of menstrual blood which produces the chocolate cyst. These cysts may vary in size from one centimeter up to six or eight centimeters in diameter, in very rare instances becoming much larger (twelve or fifteen centimeters in diameter). These cysts, after they have formed by the invasion of the endometrium, tend to perforate by extension of the endometrium again outward and cause a spillage of some of the chocolate fluid. This old menstrual blood is most irritating, and causes the cyst to become extremely adherent to its adjacent tissues. This is particularly on the undersurface of the broad ligament from the inferior and lateral portion of the ovary. Just why the perforation occurs mainly at this point is not clear. It would not seem that the original implants occurred particularly in this spot. Sampson's original title, *Perforating Hemorrhagic (Chocolate) Cysts of the Ovary,* was most appropriate in describing the characteristic finding with this cyst, which becomes densely adherent from the minute perforation. In trying to mobilize this cyst, one almost always spills the chocolate fluid when separating the perforated area that has become sealed over with the adhesion.

Beneath the wall of the chocolate cyst, or endometrial cyst, there are primordial ova, such as occur in the surface of the ovary. Hughesdon (1957) believes that the endometrial cyst forms on the surface and presses the cortex deep down into its interior, that instead of being an invasive growth it extends by pressure, sealing over its surface. From clinical appearance of the extension of the cyst into the very hilum of the ovary, one would tend to doubt this explanation.

Peritoneal implants may occur at any point in the pelvic peritoneum, particularly in the anterior cul-de-sac, over the bladder, and in the very dependent portion of the posterior cul-de-sac. Implants may occur on the round ligaments, and may invade it to form a nodule, a small adenomyoma of one or two centimeters in diameter. Surface implants may occur over the ureter and may even extend to involve the wall of the ureter, so as to cause ureteral obstruction in very rare instances.

Bowel implants are frequent. Some degree of involvement of the rectosigmoid in the cul-de-sac lesions is the rule. These implants may extend well up along the wall of the sigmoid for several centimeters, causing a marked thickening in the wall of the bowel, the endometrial glands and surrounding extensive fibrotic stroma extending well through the muscularis and pressing against the sub-

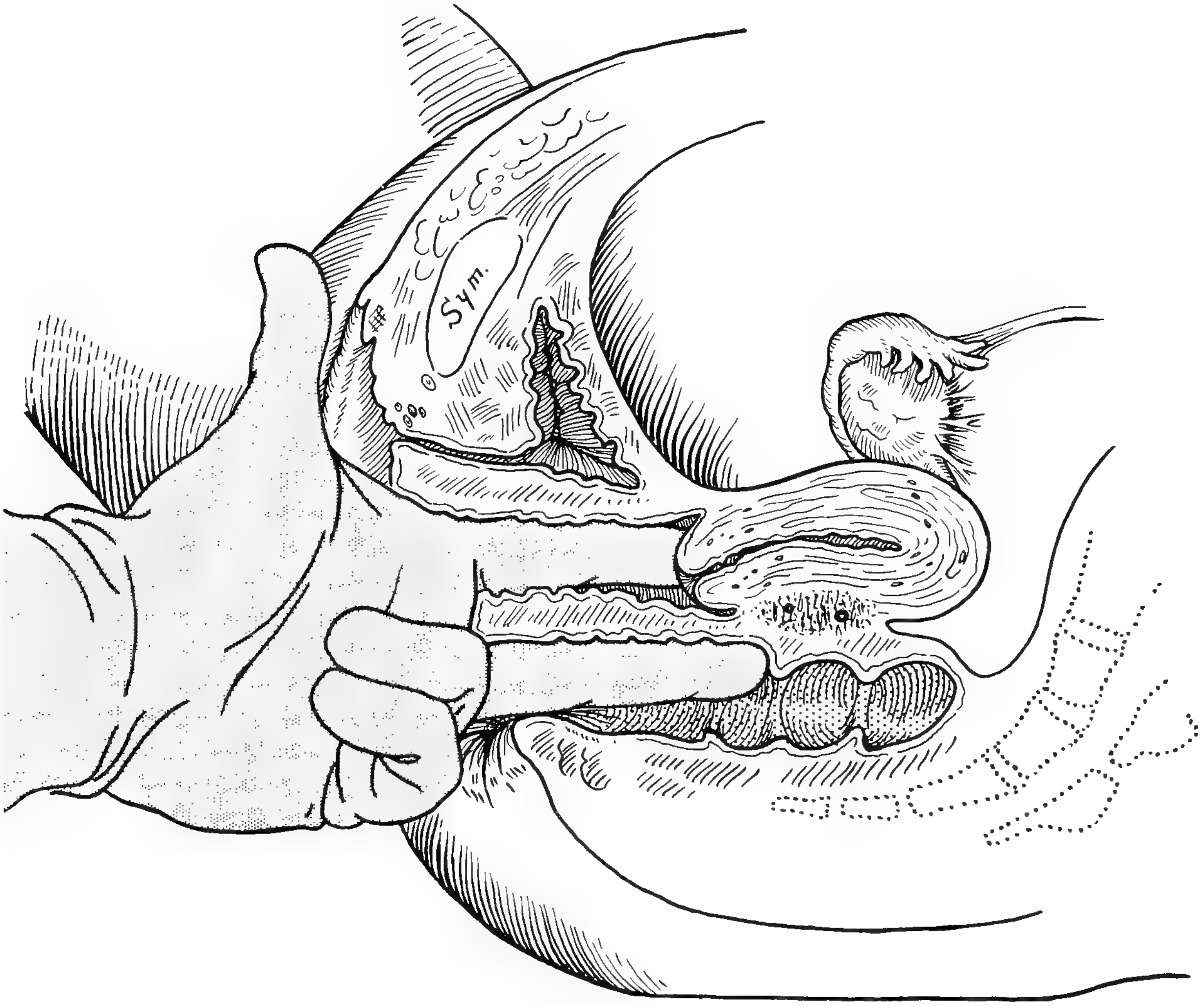


Fig. 263. Endometriosis with adherent retroversion and scarring between uterus and rectum (diagram). This quite firm, irregular and exquisitely tender endometriosis is readily diagnosed. The adherent ovary cannot be reached for palpation. Recto-vaginal examination is very helpful in palpation of the cul-de-sac for this frequently occurring disease.

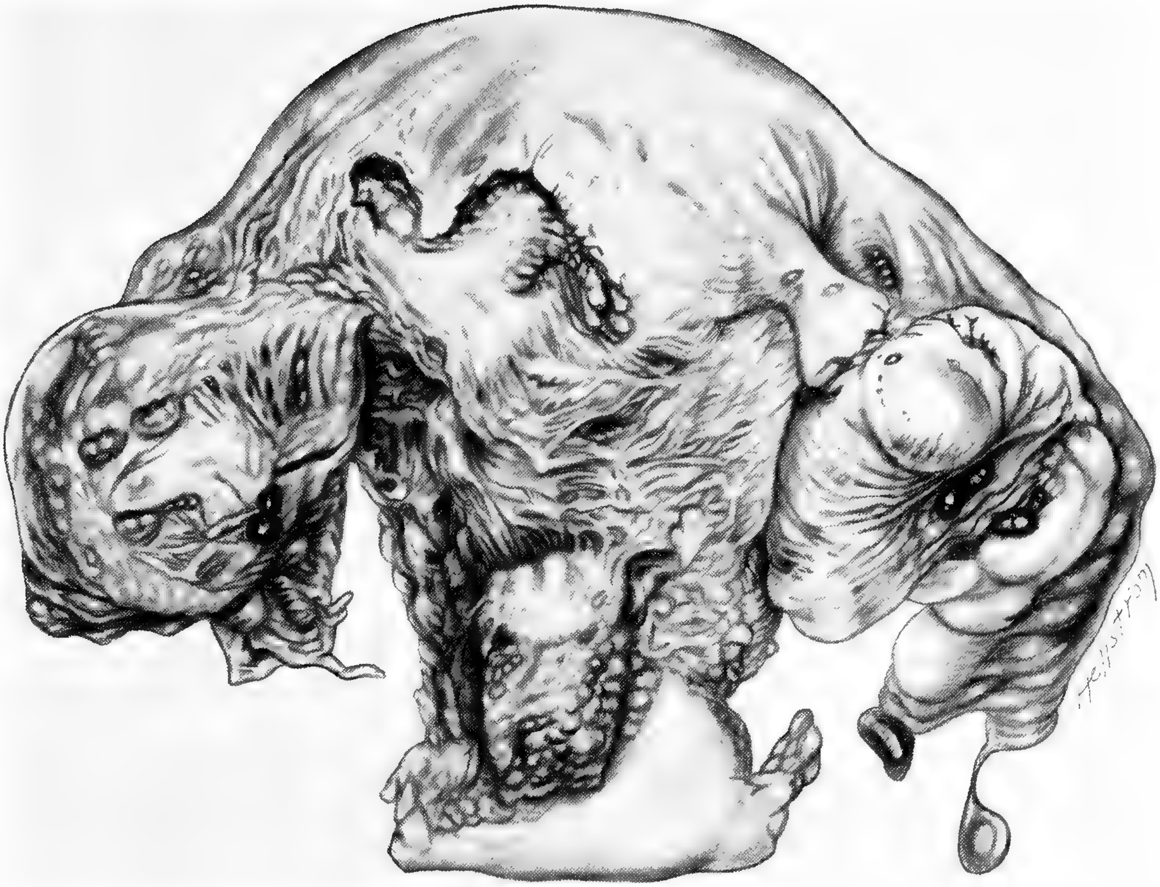


Fig. 264. Extensive endometriosis. The puckered, extremely adherent endometrial cysts which have destroyed these ovaries show the leaking of chocolate fluid from their areas of possible previous perforation. The area of marked thickening and scarring on the back of the cervix represents a sizeable mass of endometriosis which had involved the muscularis of the rectal wall. The ragged posterior surface of the uterus indicates its dense adherence to the rectal wall. The tubes are distorted but were patent.

mucosa of the bowel. Extremely rarely does the endometriosis perforate the mucosa, so that bleeding from the bowel at the time of menstruation as a sign of endometriosis is not to be expected, though this may occur in extraordinary and rare instances. In isolated areas up along the free border of the sigmoid, endometriosis may occur in a puckered area and grow deeply into the wall of the sigmoid, forming a nodule of one, two, three or more centimeters in diameter, pressing into the lumen. Such intraluminal defects may be seen in films after barium enema. These nodules, when discovered at operation, may be difficult to distinguish from carcinoma of the sigmoid. One may dissect these areas from the bowel wall down to the submucosa and relieve a marked kinking. At times it is necessary to enter the lumen to excise the lesion. Lesions of the transverse and ascending colon must be extremely rare. On the other hand, involvement of the appendix and its base is not so infrequent. Areas of typical brownish, puckered, or purplish thickening along the wall of the appendix, and particularly in its base, are found at times in patients operated on for appendiceal symptoms, without acute inflammation. On the surface of the terminal ileum, within its last three feet, there may be puckered implants of endometriosis, with marked thickening of the muscularis of the bowel, so that a nodule may press into its lumen, and often there is kinking of the bowel in this area. The kinking may be sufficiently severe to produce acute intestinal obstruction, caused by the endometrial adhesions. On more rare occasions, the endometrioma itself may obstruct the lumen of the bowel, but usually the acute obstruction is caused by the adhesions from the endometriosis.

On the surface of the fallopian tube endometriosis with purplish, puckered areas may occur and greatly contort the surface of the tube, causing constriction and angulation, with thickening in the wall of the tube itself. At times the local areas may be excised, but salpingectomy may be necessary. Within the interior of the fallopian tube, areas of endometriosis are not unusual, and are thought by some to be a possible etiologic agent for tubal pregnancy, attracting the fertilized egg to the bed of endometrium. That these areas may arise from implantation seems less likely than that they may develop from the multipotentialities of the mullerian epithelium. The rather frequent finding of areas of endometrium in the fallopian tube, and the occurrence of tubal-like mucosa in the endometrial cavity suggests that these are congenital changes that occur within these two areas.

Endometriosis of the umbilicus has been reported not infrequently in the literature, occurring as indurated areas in the umbilicus, having a purplish appearance, associated with recurrent pain at the time of menstruation and perhaps perforating and draining menstrual blood at that time. These lesions may be associated with no other endometrial implants in the pelvis. In such instances, one suspects that they may be misplaced in the umbilicus; or, that the implant may have transferred from the endometrium to the umbilicus by means of the lymphatics. Endometrial implants on the surface of the bladder are quite frequent and may extend into the muscularis by extension; occasionally the lesion presents itself into the interior of the bladder and may perforate the mucosa, causing hematuria at the time of menstruation. Symptoms of cystitis with menstruation are present. The condition is diagnosed by finding the projecting, purplish-red area with the cystoscope. Endometriosis in lymph nodes has been reported in several instances, and somewhat more frequently in lymph nodes in the pelvis. Recently, Javert has reported five such instances found in the course of pelvic lymphadectomy. Endometriosis in the inguinal canal has been found on occasion; it forms a mass which is painful at the time of menstruation, and may suggest an incarcerated hernia. Exploration shows typical brownish puckered implants of endometriosis with varying degrees of fibrosis in the end of the round ligament, or within a cyst at the end of the round ligament. This is not associated directly with the peritoneal cavity, or with an inguinal hernia, although an opening was present in embryonic or in fetal life, which was sealed over later. A possible connection might be present, as a minute inguinal hernia, which would allow retrograde menstruating epithelium to become lodged within such a tiny non-visible sac. One is more prone to accept a serosal origin in these instances. The presence of endometriosis in laparotomy scars, when operations are performed on the uterus, especially following Caesarian sections, certainly makes one think that implantation of epithelium occurred to cause this lesion. The subcutaneous tissue becomes quite thickened, swells, becomes painful with menstruation, and tends to perforate and to drain menstrual-type of blood externally at the time of menstruation.

Implants of endometriosis have been described in the cervix as a primary lesion in a few instances, and more often as a secondary lesion, the endometriosis perforating the posterior wall of the vagina and growing onto the posterior wall of the cervix, forming typical bluish cysts with characteristic hard, nodular scar tissue about them. It is remarkable how often bright red spots, or minute bluish cysts on the surface of the cervix are found after radial cauterization, or after biopsy of the cervix. One wonders if this secondary implantation may be related to the time of the oncoming menstrual period, but since the cervix remains unhealed for a few weeks following these procedures it seems unlikely that the relation to the menstrual cycle could be too important. These minute cervical lesions never extend to any great degree, and are entirely asymptomatic. They are of interest from a diagnostic point of view. As mentioned, endometriosis of the vagina more frequently is present as perforation of nodules from implantation in the cul-de-sac. This has been called adenomyosis of the rectovaginal septum. The marked nodular growth in the posterior fornix of the vagina is characteristic and diagnostic of the condition, especially if one can see the purplish, cystic changes. Minute red spots throughout the vagina are seen at intervals, and represent small implants. Other areas of endometriosis of the vagina follow surgical procedures, especially that of episiotomy. A number of reports have described endometrium in the upper portion of the episiotomy incision in the vagina and

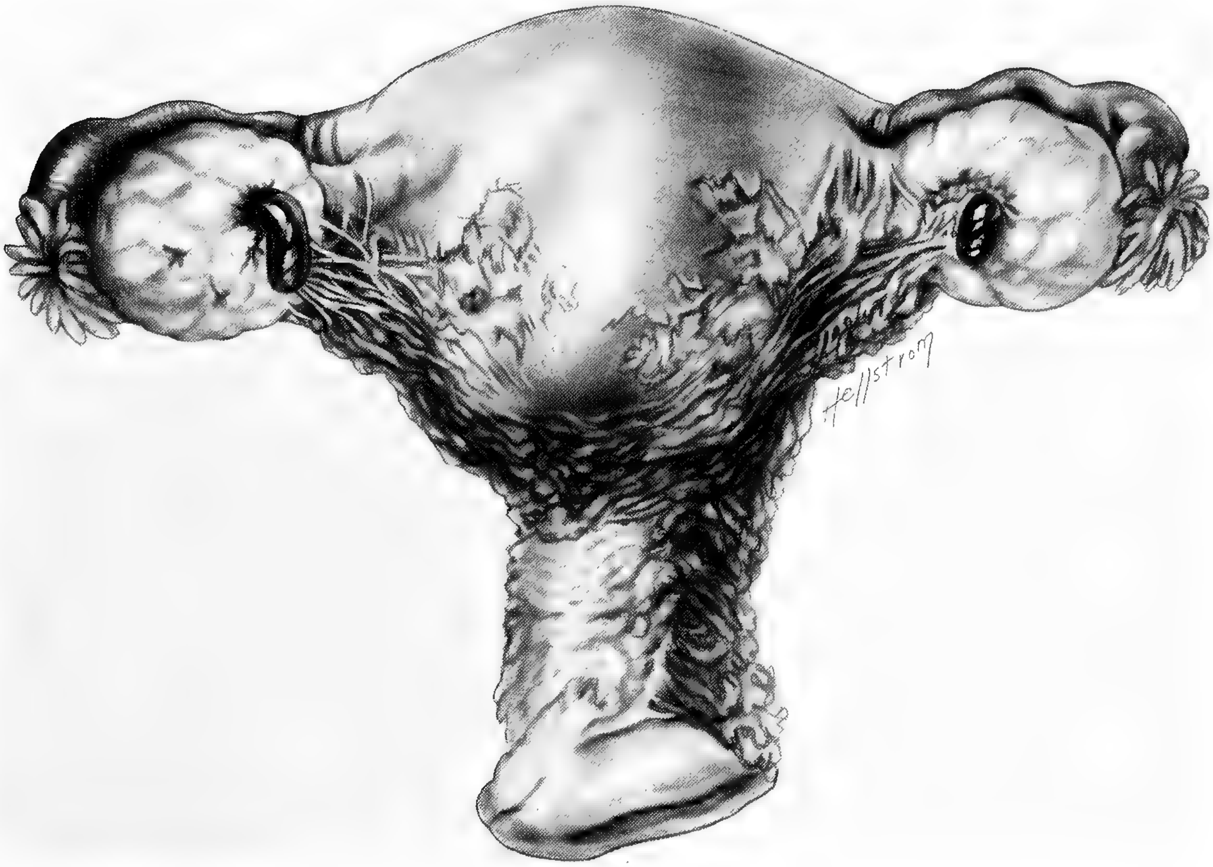


Fig. 265. Endometriosis involving the ovaries, posterior wall of the uterus and cervix. The small endometrial cysts had been densely adherent to the sides of the uterus and posterior leaf of the broad ligaments. In their mobilization, the cysts were torn open and liquid chocolate-like fluid was extruded. The sigmoid was adherent to the posterior wall of the uterus. In the young woman desirous of children, these ovaries might have been resected, the uterus suspended, and pregnancy may have resulted. Continued growth of endometriosis may have required a second operation.

in the lower portion of the perineum, which becomes painful with menstruation and which may open and drain chocolate fluid.

Primary endometriosis of the vulva has been described in a very few instances, but secondary endometriosis more frequently has occurred after the excision of the Bartholin's gland for cyst or abscess. Apparently implants must get into the incision, and occasionally form these areas of endometriosis.

In 1926, Navratil and Kramer presented an exciting case of endometriosis of the bracheoradialis muscle. Much conjecture has been offered since that time as an explanation for the case. For a long time, no other extraordinary cases were reported, until Marshall reported one in the kidney in 1943. Presumably, this may have arisen by lymphatic metastasis or by congenitally placed celomic epithelium, which had the capabilities of developing into endometrium in adult life. In 1944, Schlicki reported a case of endometriosis in the thigh in a Filipino woman. Since then, three or four cases have been reported in the pleura and lung. The one which is most acceptable is that of a deciduoma of the lung occurring during pregnancy, forming a well-defined, discrete and encapsulated tumor. One would wonder if this might be related to the normal metastasis of chorionic villi, which might have carried a portion of decidua to its destination.

Microscopic study of the implants of endometriosis reveals endometrial glands, surrounded by stroma. Nearly always is found the interval non-secretory phase. These multiple small areas as a rule show little or no secretory change during the progestational phase of the cycle, although in some instances there may form typical premenstrual endometrium. However, during pregnancy a decidual change is the rule, evidently because of the great increase in progesterone over that found in the regular menstrual cycle. In fact, the formation of very numerous, minute areas of decidua over the uterus, around the ovaries, on the pelvic peritoneum, so commonly seen at Caesarian section, certainly tends to indicate that there are cells from celomic epithelium remaining in the pelvis of the adult that have the potentiality of developing into endometriosis under intense hormone stimulation. This supports Novak's thesis of origin. In the non-pregnant state, the nodules in the rectovaginal septum, in the uterosacral ligaments, and in the bowel wall, show great proliferation of fibroblastic tissue and apparently some smooth muscle, in the centers of which there are scattered islands of endometrial stroma and glands. In these small glands, there may be areas of disruption of the epithelium with the accumulation of old blood. Evidently this represents some degree of bleeding during menstruation. Since areas of endometriosis do not go through a secretory cycle as a rule, implants seem to represent the basalis of the endometrium, and not the functional, superficial portion of the endometrium which responds to the physiologic amounts of progesterone after ovulation. The endometrial cyst of the ovary may be lined by well formed endometrium having a surface epithelium, stroma, and glands, but this is relatively rare. Much more commonly only small portions of the wall are lined in this manner, and the larger portion of the cyst is lined with only fibrous or fibroblastic tissue, with hemosiderin-containing cells from the absorption of the blood in that area. It may be quite difficult to find true endometrium in the wall of the endometrial cyst without numerous blocks. Often, one can determine only that it is a hemorrhagic cyst, and cannot say positively that there is endometrium in the lining, but such a cyst, one that has been adherent, has perforated, has the typical appearance, is surely an endometrial cyst. At times the chocolate cyst may represent an old hematoma from a corpus luteum, and this old blood may have the same chocolate color, but the corpus luteum hematoma should never be adherent, because it is not the perforating type. It should be freely mobile, and it does contain the yellow border in the wall which suggests grossly that it represents a corpus luteum in its origin, perhaps a month or several months old. Again, the functional cycle of the endometrium is rarely seen in the endometrial cyst, or in other implants on the ovary, although occasionally a secretory change is seen, or even full-grown premenstrual change. On the other hand, during pregnancy, within the wall of the endometrial cyst and the implants on the surface of the ovary, there is a change in the stroma to decidua, so that the cells become quite large, swollen, and filled with glycogen. This is because of the extremely large amount of progesterone, along with a certain amount of necessary estrogen, which causes this appearance.

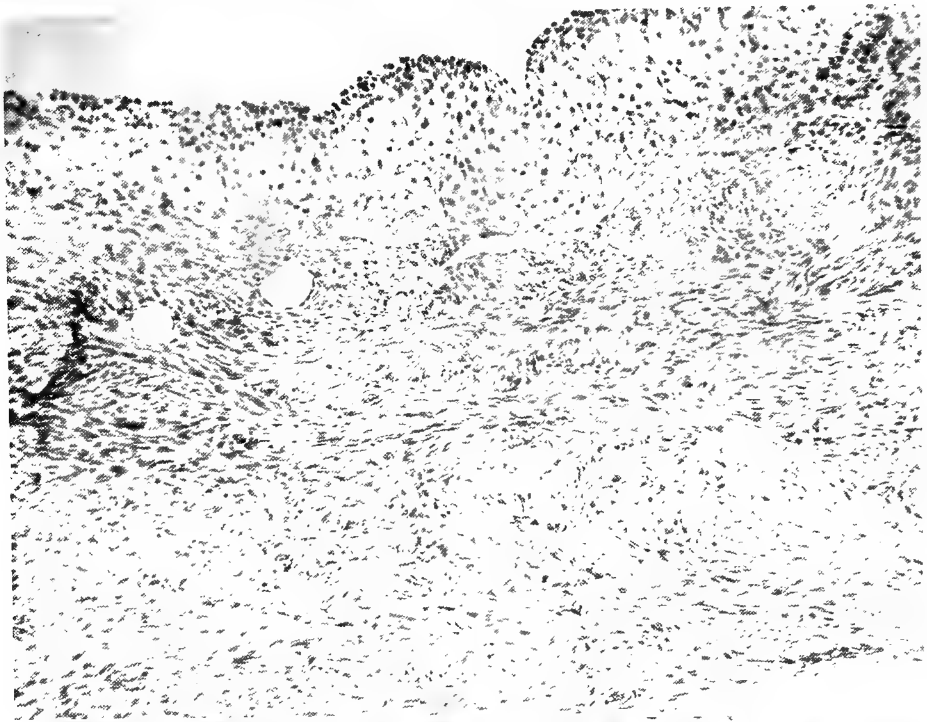
Malignant changes in endometriosis are apparently quite rare. Only about twenty-five cases have appeared in the literature over the past forty years, and in several of those there may be some question. To be reasonably sure that an adenocarcinoma in an ovary or in the pelvic peritoneum has arisen from endometriosis, the tumor must be connected by continuity with non-malignant endometrial cells, and there must be no other obvious explanation for the tumor, such as an adenocarcinoma of the endometrium or other origin. These criteria make it difficult to say that a particular adenocarcinoma has this origin. Perhaps many more do arise in this manner, but are never proved. The general opinion is that endometrial implants exceedingly rarely become malignant, far less commonly than endometrium inside the uterus. Certainly, adenocarcinoma arising in the rectovaginal septum, or uterosacral ligaments, or in other implants, have been reported with the greatest rarity.

It is of considerable interest that the majority of tumors that have been reported in the ovary as a malignant change of endometriosis have the microscopic characteristic of adenoacanthomas. This is a form of adenocarcinoma with areas of metaplasia in the squamous cells. Actually the squamous cells seem truly metaplastic and perhaps not malignant, at least they do not have the malignant appearances of ordinary squamous cell carcinoma. It seems that this is a rather characteristic finding, though not all the cases have had this. When adenoacanthoma occurs in the ovary, it is suggestive that it may have arisen from endometriosis, although not necessarily so.

SYMPTOMS

The symptoms of endometriosis depends much on the position of the endometrial implants, but is characteristically that of pain or discomfort or bleeding coincidental with the menses. The most frequent complaint with endometriosis is that of pelvic pain. This pain may occur at the onset of menstruation, as intermenstrual discomfort, bearing-down, pressure pain, and heaviness in the pelvis. Increased pain at the time of menstruation is a most frequent symptom, though by all means not unanimously present. The dysmenorrhea of endometriosis characteristically begins after the age of twenty-five years, although the disease is certainly found frequently in women under twenty-five years of age. This acquired menstrual pain has a different character than that of functional dysmenorrhea. In functional dysmenorrhea, the pain is described as cramping, as a rule located in the midline, or deep in the pelvis. The pain of endometriosis is more to the sides of the pelvis, and more of a constant type of pain, in contrast to cramping, and is frequently described as "grinding." Often it has a lightning or nerve-like character, shooting through the rectum. The patient may have the sensation of desire to defecate, and of intense pressure discomfort in the rectum, so that she must strain at the stool. Symptoms apparently are caused by swelling and bleeding of the endometrial implants wherever

Fig. 266. Endometrial cyst, low power view. The surface epithelial layer is partially intact in the lining of this chocolate cyst. Beneath it there are large, foam-like cells suggestive of lutein cells, frequently found in the endometrial cyst which confuses the origin on occasion.



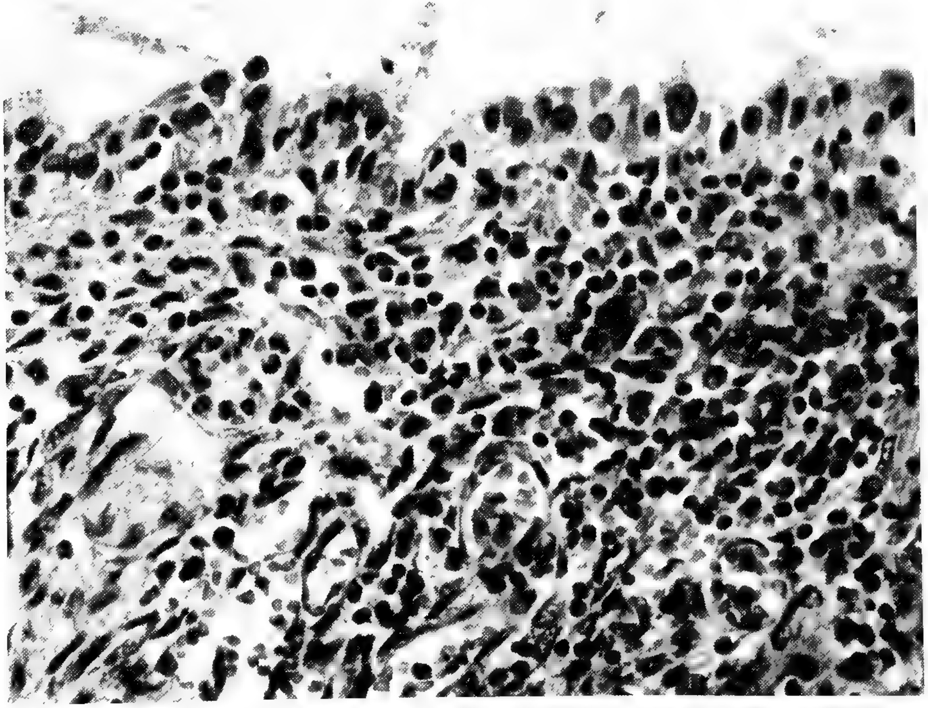


Fig. 267. Endometrial cyst of the ovary, high power view. The surface epithelium is intact. Some of the nuclei certainly vary in size and shape. Inflammatory cells have infiltrated the wall of the cyst in this area.

they may be placed, and since they are most frequent in the posterior cul-de-sac and involve the surface of the rectum, it is logical to expect these rectal complaints. At times rectal pain is present for two weeks before menstruation, or even throughout the month. Severe diarrhea may occur with menstruation, and rarely this may continue throughout the month, being caused by endometriosis of the bowel wall. Abnormal uterine bleeding is extremely frequent with endometriosis. More than half of the patients complain of prolonged and heavy menstruation. The menorrhagia may be related to nervous tension in some instances, to additional pathology, as small myomas or adenomyosis, or to hormone imbalance. At any rate, the abnormal menstruation is a frequent and annoying difficulty for patients with endometriosis. Intermenstrual bleeding and metrorrhagia, irregular and prolonged bleeding, also are not infrequent with early or late endometriosis. Dyspareunia is a frequent complaint, with its associated frigidity, the symptom being caused by endometrial implants in the cul-de-sac and uterosacral ligaments, which are extraordinarily tender to examination and for the deep penetration of sexual intercourse. The symptoms are worse with the frequent adherent retroversion of the uterus, especially with the nodulations of endometriosis beneath it. Sterility may be a not infrequent complaint with endometriosis. By no means are all patients with endometriosis sterile. In fact, in a large series of patients, more than fifty per cent of them with extensive endometriosis, sufficient to require radical surgery, had had children. On the other hand, of young people as a separate group who have adherent retroversion and nodulations of endometriosis in the pelvis and adherent ovaries, a larger per cent may complain of sterility. In fact, about fifty per cent of these young people have a definite complaint of sterility, may have been observed and treated for two and three years, and finally may be treated by conservative surgery with subsequent fertility in half of the cases. Just how the sterility is produced is not clear, because almost all of these patients with external endometriosis do ovulate, and almost invariably the fallopian tubes are open. The symptoms of endometriosis in other areas than in the pelvis include pain, swelling, and possible bleeding of the area in which the endometriosis has occurred. Often, it is thought that patients with hemoptysis, or with bleeding from the rectum, or from the nose, occurring with menstruation, must have endometriosis in the location. Endometriosis has never been discovered in anyone's nose, although an extraordinary number of women have complained of nasal bleeding at the time of menstruation. Undoubtedly, this must be related to some increased capillary fragility at that time, or to nervous tension. While the symptoms suggestive of endometriosis may be impressive, and in fact helpful in drawing one's attention to the possibility of endometriosis, and even in aiding in the diagnosis, coincidental bleeding from other parts at menstruation may lead one entirely astray. The patient with the most characteristic complaints of acquired dysmenorrhea, of pains in the sides rather than in the center of the lower abdomen, or constant, "grinding-type" of pain that shoots into the rectum, a severe degree of the intense desire to defecate, a severe bearing-down sensation, surprisingly may have no palpable pathology, and may have no pathology on exploratory laparotomy. This has been the experience of many surgeons; one must be wary of the "arm chair" diagnosis of endometriosis. Always the cyclic recurrence of symptoms, pain, and the presence of a mass which becomes tender and enlarged, and the plausible association of bloody drainage, are suggestive of endometriosis. But, symptoms without positive palpable evidence of nodulation and tumor-formation are never diagnostic of endometriosis.

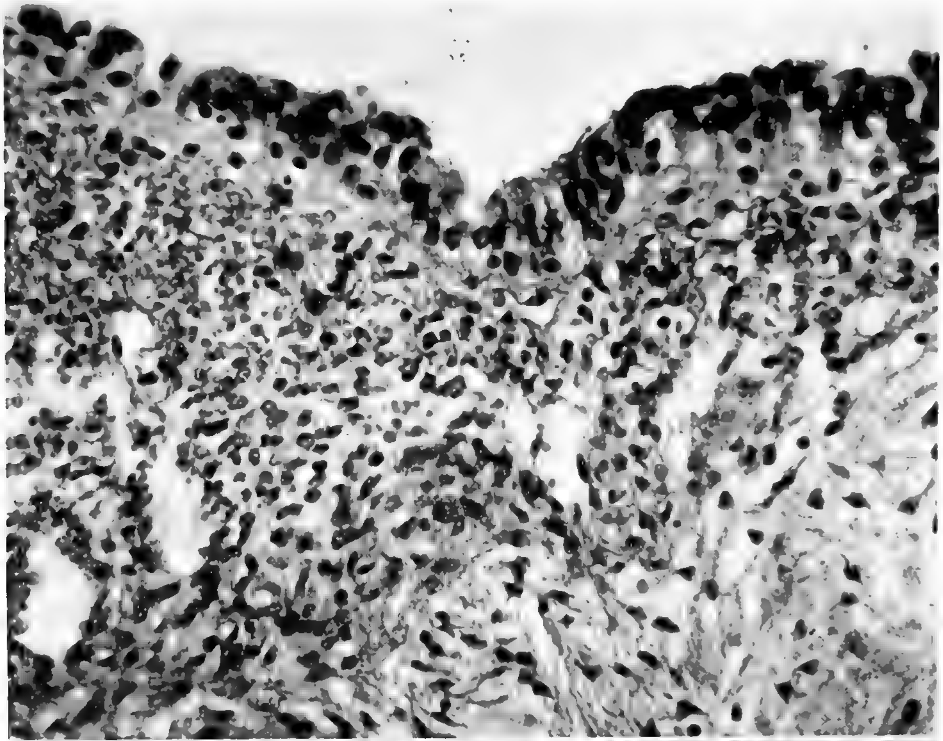
DIAGNOSIS EXTERNAL ENDOMETRIOSIS

The diagnosis of external pelvic endometriosis is made by the finding of B-B shot nodules in the cul-de-sac, or the palpation of nodulations in one or both uterosacral ligaments, which are quite hard, irregular feeling, have a barbed character, and measure one, two, or three centimeters across. Sometimes these areas are found only by rectovaginal examination, placing fore finger in the vagina and the third in the rectum, allowing one to feel the posterior cul-de-sac more accurately in this manner. If there are surface implants without enlargement of the ovary, commonly the ovary becomes adherent because of the irritating effect of the menstrual blood from the surface implants. Any adherent or immoveable ovary of normal size may represent endometriosis or chronic salpingitis with adhesions of the ovary. The former is diagnosed by the telltale evidence of B-B shot implants or areas of barbed induration in the uterosacral ligaments. An adherent ovarian cyst is produced by endometriosis of the ovary which has perforated slightly and caused subsequent dense adhesions, or by the adhesions from pelvic inflammatory disease, or by adhesions from a malignant cyst of the ovary. The first diagnosis is confirmed, or assumed, by the presence of endometrial implants in the cul-de-sac and uterosacral ligaments, which may be reasonably accurately determined. Sometimes, induration in the uterosacral and cardinal ligaments has resulted from inflammation in the cervix or the fallopian tubes, and sometimes induration in the cul-de-sac is related to metastatic malignancy from the ovary or from the stomach or intestinal tract. As a rule, however, one can distinguish endometriosis by the extraordinary tenderness of the discrete, shotty areas in the cul-de-sac and along the uterosacral ligaments. The presence of the retroversion, usually adherent, with endometrial implants that are palpable in the cul-de-sac is another corroborative evidence of endometriosis in those cases. By no means do all patients with retroversion of the uterus have endometriosis, but of those with endometriosis in the young about eighty per cent have retroversion of the uterus. After the age of thirty-five years, only about ten per cent have retroversion of the uterus. The only explanation of this is the presence then of large endometrial cysts or myomas of the uterus, which must have pressed the corpus of the uterus forward, because one cannot explain the adherent retroversion moving forward any other way. Certainly adhesions to the bowel in the late endometriosis case, even with the anterior uterus, is a frequent finding, but the large endometrial cyst which leaves no room for the retroversion is a most frequent finding also with late endometriosis.

Some have advised the use of culdoscopy to determine the presence of endometriosis when it is not readily palpable and not clearly diagnosed. The insertion of this sheath through the posterior vagina in the knee-chest position, after pressing a very sharp-pointed dagger through the sheath to open into the abdominal cavity, has seemed dangerous to many, because of the frequency of adhesions of the bowel to the back of the cervix and uterus. Also the frequency of retroversion with its associated adhesions makes this tool of infrequent value in the examination of the pelvic organs in cases with endometriosis.

The diagnosis of endometriosis is made in some instances by seeing the endometrial implants on the cervix where the implant has a bright red color, or a purplish raised area about the cervical os, almost always having followed biopsy and cauterization of the cervix. Implants in the posterior cul-de-sac may be present in the posterior fornix of the vagina and protrude into the vaginal canal as gross nodulations which may show bluish cysts beneath the thick vaginal epithelium. Areas in the vagina and vulva form nodules with superficial granulations, or a sinus tract becomes

Fig. 268. Endometrial cyst showing a fairly intact epithelial lining area, two, three or four layers thick. Beneath the epithelium there is some stroma which may be distinguished and there is hemorrhage. The wall of the cyst shows the marked fibrous type of tissue, characteristic in this condition.



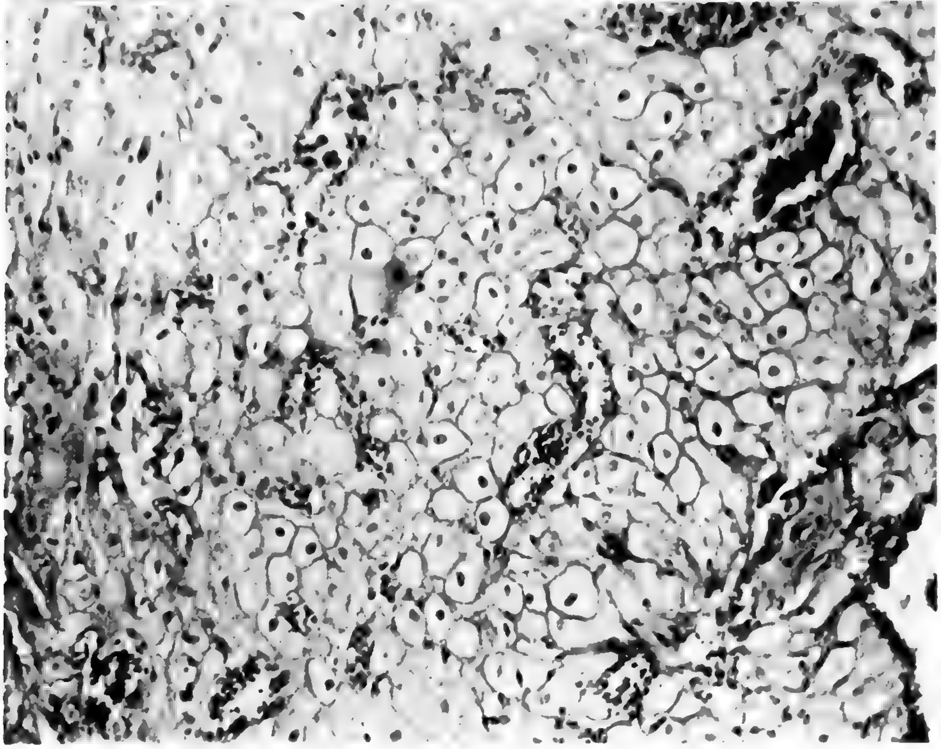


Fig. 269. Endometriosis of surface of ovary with decidual change. Biopsy was taken of the pink, velvety area at Caesarian section.

larger, more tender, and may bleed with menstruation. Many times nodules in any area of the pelvis that seem to enlarge and become more symptomatic with menstruation turn out not to represent endometriosis at all. The reason is that all genital tissues become more congested, more edematous, and more symptomatic with menstruation.

EXTERNAL ENDOMETRIOSIS: TREATMENT

The treatment of endometriosis may be classified as *observation, pregnancy, hormones,* and *surgery.* Actually, one could hardly say that observation is treatment, and one could hardly say that pregnancy, a normal and physiological action, is a treatment. However, observation does mean that while endometriosis is diagnosed frequently in women, not always by any means is any operative treatment indicated. The finding of the typical, shotty nodules in the cul-de-sac, the typical induration in the uterosacral ligaments, the finding of an adherent ovary, or adherent retroversion, or even the finding of a small, adherent endometrial cyst of three, four or five centimeters in diameter, are no indications for treatment if there are no symptoms, as excessive bleeding, severe pain, and sterility that does not respond to ordinary conservative measures. Just because there is endometriosis present does not mean that surgery is necessary, or that any interference is indicated. If there is no serious dyspareunia, disturbing to the stability of a marriage, if there is no incapacitating dysmenorrhea, or other serious abnormal symptoms, then these patients are better treated by reassurance, analgesics for menstrual discomfort, and reexamination at intervals. The endometriosis may remain at a status quo for very many years, and, in fact, may never seem to increase. On the contrary, in the course of six

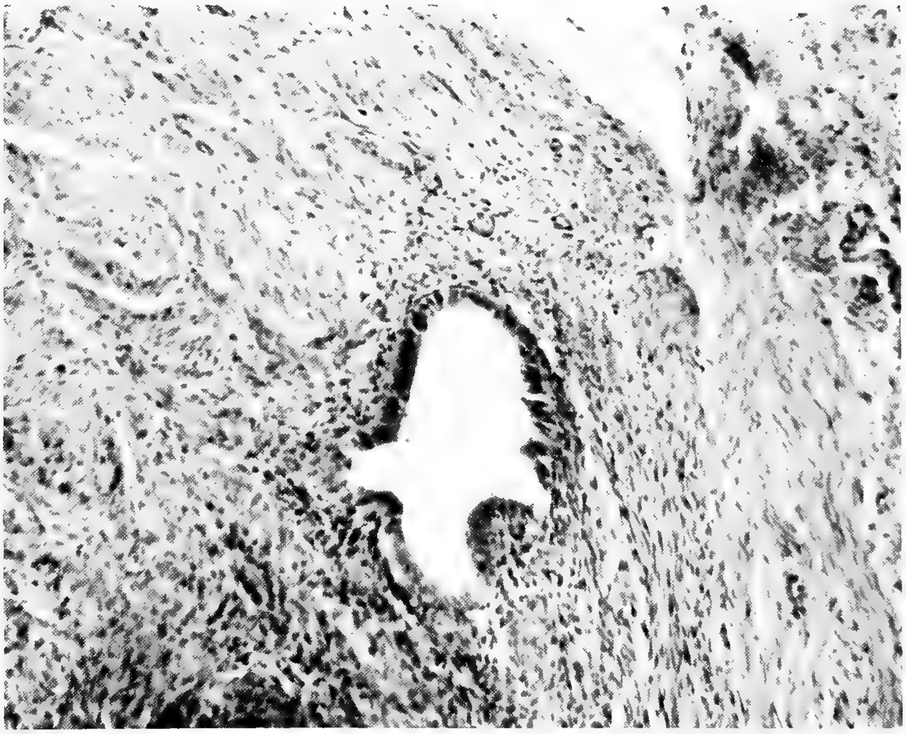


Fig. 270. Endometriosis from cul-de-sac. The nonsecretory gland is surrounded by stroma, and there is marked proliferation of fibrous tissue and smooth muscle. Infrequently are cyclic changes seen in these implants. The large amount of progesterone in pregnancy does cause a decidual change.

months to a year, it may increase to a serious and severe degree, requiring active interference. It may remain quiescent for fifteen or twenty years, and then develop into serious and extensive endometriosis. The very normal physiological event of pregnancy can hardly be considered a treatment, but if it is true, as many have felt, that pregnancy causes endometriosis to disappear, or, at least, to improve in considerable degree, or not to extend for a period of years, then the pregnancy must have a beneficial effect. Others believe that endometriosis is not cured in any degree by pregnancy, although it is softened greatly by the decidual change in the stroma; the pregnancy hormones do affect the fibrous tissue and smooth muscle surrounding the implants and cause a marked softening. Following pregnancy and delivery, some have felt that the endometriosis was improved, and others have felt that it has returned precisely to its same situation and that it may even be worse. Endometrial cysts have become enlarged and painful during pregnancy and have required excision. In several reported cases, these cysts have ruptured, causing severe and acute catastrophic abdominal pain with degrees of shock, requiring operation. In the usual case of endometriosis, evidently the cysts do not rupture or cause any increased or severe pain during pregnancy. The more important point is that of having a child for its own sake, rather than the purpose of having a pregnancy in order to try to cure a disease. It is always distressing to hear a patient ask if another pregnancy could be expected to cure nervous or organic complaints, and if so that she might decide to have another child. The purpose of pregnancy is that of having a child, and not an excuse to cure a disease, although great physiological changes may occur during the time of the pregnancy.

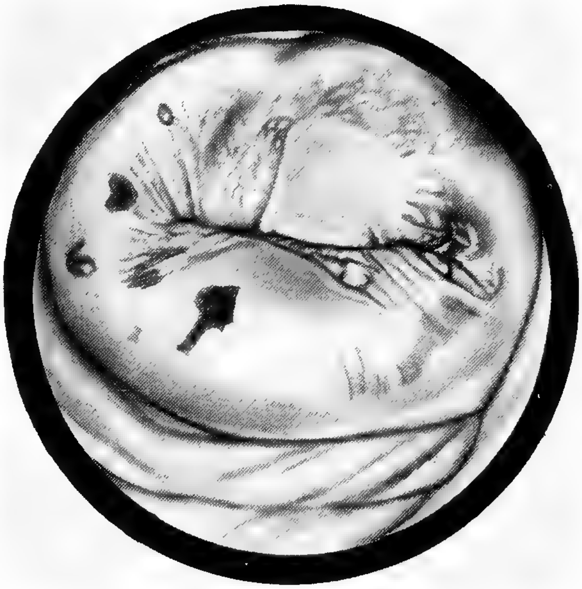


Fig. 271. Endometriosis of cervix. The dark, slightly raised areas around the periphery have a purplish-red color and indicate endometriosis. The dagger-like area represents a biopsy. In addition, there is a moderate eversive cervicitis, with small lacerations.

The third treatment to be considered is that of hormone therapy. In 1948, Karnaky suggested that large doses of stilbestrol, a synthetic estrogen, would cure endometriosis, and since that time this treatment has been used widely. However, there are relatively few reports in the literature to establish the credibility of this treatment. A few authors have felt strongly that endometriosis is not cured or helped in any degree by estrogen therapy. Others feel that the estrogen has helped, but seem to have an impression other than a conclusive opinion. While it is known that large doses of testosterone will stop menstruation, will neutralize estrogenic hormone, will depress pituitary action, prevent ovarian secretion of hormone, and will cause atrophy of the ovary temporarily, and as such will cause endometrial implants to regress, cause endometrial masses in the cul-de-sac to become exceedingly small, it is true and to be expected that they will always recur if the testosterone is discontinued and the ovary allowed to return to its normal estrogenic action. Probably the endometriosis would require some months to return to its original size. From the amount of testosterone necessary to neutralize these estrogenic effects, there would develop a most marked

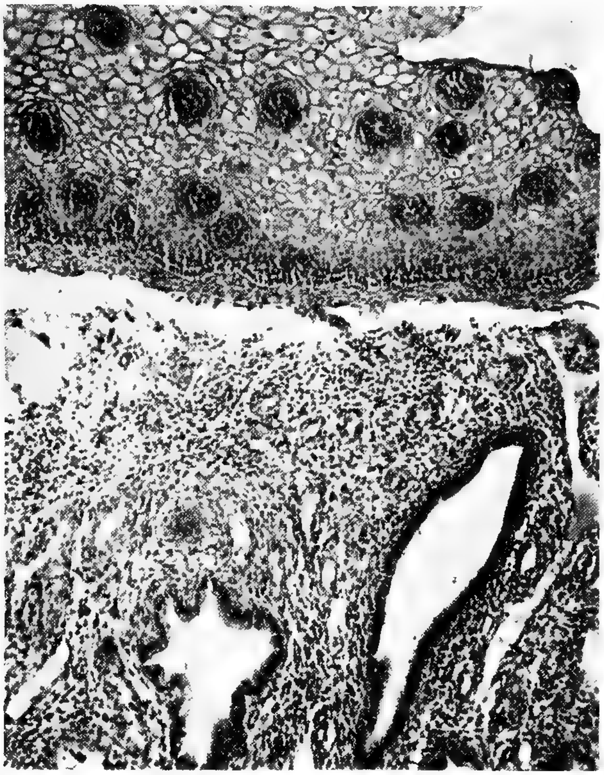


Fig. 272. Endometriosis of cervix. Beneath the stratified squamous epithelium (with rete pegs cut tangentially) are typical endometrial glands and stroma. (From case in Fig. 15.)

virilization of the patient, as a heavy growth of hair on the face, a deep voice, acne of the skin, atrophy of the breasts, and marked enlargement of the clitoris. Even the use of so-called non-androgenic androgens also have an androgenic effect, enough to be entirely undesirable in this benign disease. In the treatment of malignant disease, as carcinoma of the breast, perhaps the virilization is of somewhat less importance. After the demonstration by Miller of the effects of strong testosterone therapy, Creadick, followed by a number of others, have advised the use of methyl testosterone in five or ten milligram doses daily for two, three or four months or longer. These amounts do not interfere with ovulation, do not prevent pregnancy, and this therapy is said to cause atrophy of the endometrial implants and relief of pain. It is difficult to understand how a patient can have an essentially normal amount of estrogen, enough to be able to become pregnant, and yet can have an interference with estrogenic stimulation not only to prevent growth of the endometriosis, but to cause atrophy. There remains doubt as to the effects of this treatment. Kistner (1959) recently has reported on the use of long-acting injectible progestational compounds and of the extremely potent oral protestational compounds in the treatment of endometriosis. His thesis has been that pregnancy causes endometriosis to regress, or to be cured, and that the formation of a pseudo-pregnancy may cure the disease. He has used particularly norethynodrel with ethynil estradiol (Enovid) in doses of ten to forty milligrams daily by mouth for six to eight months, and has found marked regression of the endometriosis with improvement in the patient's symptoms. Pseudo-pregnancy is produced. The patient gains ten to twenty pounds. The breasts become enlarged and full. The vulva and vagina are congested (Chadwick's sign). The cervix is soft and bluish. The uterus becomes enlarged to the size of a ten or twelve weeks pregnancy. Endometrial masses become much softer. Generally the patient feels very well during the treatment, although a few have nausea from the ethynil estradiol. If pregnancy does cure endometriosis; and many believe that it does or at least arrests its progress, then this therapy is logical and good results may follow. But there remains a doubt in the minds of many that pregnancy (and progesterone) ever cures endometriosis, or even aids its regression.

SURGICAL TREATMENT

Conservative surgery

Conservative surgery is indicated in every gynecological situation, if possible. There are certain circumstances, such as malignancy, that make radical surgery necessary; also, certain tumors, severe inflammatory conditions, and extremely severe involvement of endometriosis, leave no choice than total excision of the pelvic organs. Especially is conservative surgery indicated in young women, when surgery is necessary, and especially when the patient has not had her children. The indications for surgery are distressingly severe symptoms, which includes pain, either intermenstrual pain or severe incapacitating dysmenorrhea, which may continue for several days and interrupt the normal pursuits of that individual's life, or severe discomfort during sexual intercourse. Marked bleeding, as menorrhagia or metrorrhagia, may precipitate major surgical operations. Finally sterility, when investigation, treatment and observation over a period of time have not given a desired result, may be a strong factor for operation. This includes the investigation of the semen to rule out the male factor, the determination of tubal patency by the Rubin's test and hysterosalpingography, and finally the study of cervical secretions by the Sims-Huehner test, to determine the motility of the sperm in the cervical secretions. If these tests are within normal limits, and if pregnancy is not followed within a reasonable period of time of six months or one year, or perhaps longer, then operation may be indicated if the findings are obvious and definite, and particularly if they include an adherent retroversion and nodulations in the cul-de-sac.

The conservative operation is a more-or-less standard one. It includes first dilatation and curettage of the uterus, because the cervical canal should allow proper drainage; the endometrial cavity is investigated for polyps, myomas and septa; the endometrium is removed to determine its normal development in microscopic studies, or abnormalities; and finally the cervix is biopsied for the record and cauterized if necessary. Papanicolaou cytology studies are indicated, especially before operative procedures.

After the investigation of the lower genital tract by this portion of the operative procedure, a low midline incision exposes the abdominal cavity. After exploring the abdomen as a routine, the pelvic organs are observed in detail. In young women with relatively early endometriosis, but not necessarily minimal, the uterus is retroverted in almost eighty per cent of cases, and commonly is adherent to the rectosigmoid. The tubes invariably are open, except they may be severely kinked by endometriosis on occasion. The ovaries may be normal, may contain superficial implants, or may contain an endometrial cyst on one or both sides, which causes the ovary to become extremely adherent to the undersurface of the broad ligament. The adhesions are mobilized between the uterus and the rectum. Often in the depth of the pelvis are found multiple endometrial implants forming nodular thickened areas with typical minute bluish cysts, or brownish granular puckered growths, particularly across the cul-de-sac and in one or both uterosacral ligaments. In mobilizing the adhesions about the ovaries, usually chocolate fluid, which represents old menstrual blood from the endometriosis within the ovary, is spilled. Every effort is made to excise an endometrial cyst, if it is present, by cutting into the ovarian tissue down to the capsule of the cyst and enucleating it from the normal ovarian tissue. Sometimes the cyst has extended well into the hilum of the ovary, and it is apparently impossible to save any ovarian tissue. But the more one tries to be conservative and save a portion of ovary, the more often it may be accomplished. It is surprising how small an amount of ovarian tissue may be able to produce an egg which may be fertilized and carried to term. If implants alone are present on the surface of the ovary, these may be removed with the electric loop or with a sharp scalpel, followed by interrupted or continuous suture as necessary. In the depth of the pelvis, the areas of endometrial implants are removed as completely as possible, using the long Metzenbaum dissecting scissors. With care, much or seemingly all of the endometriosis may be removed. There may remain some scarring in the wall of the bowel or the undersurface of the broad ligament, which often may completely absorb after the more superficial por-

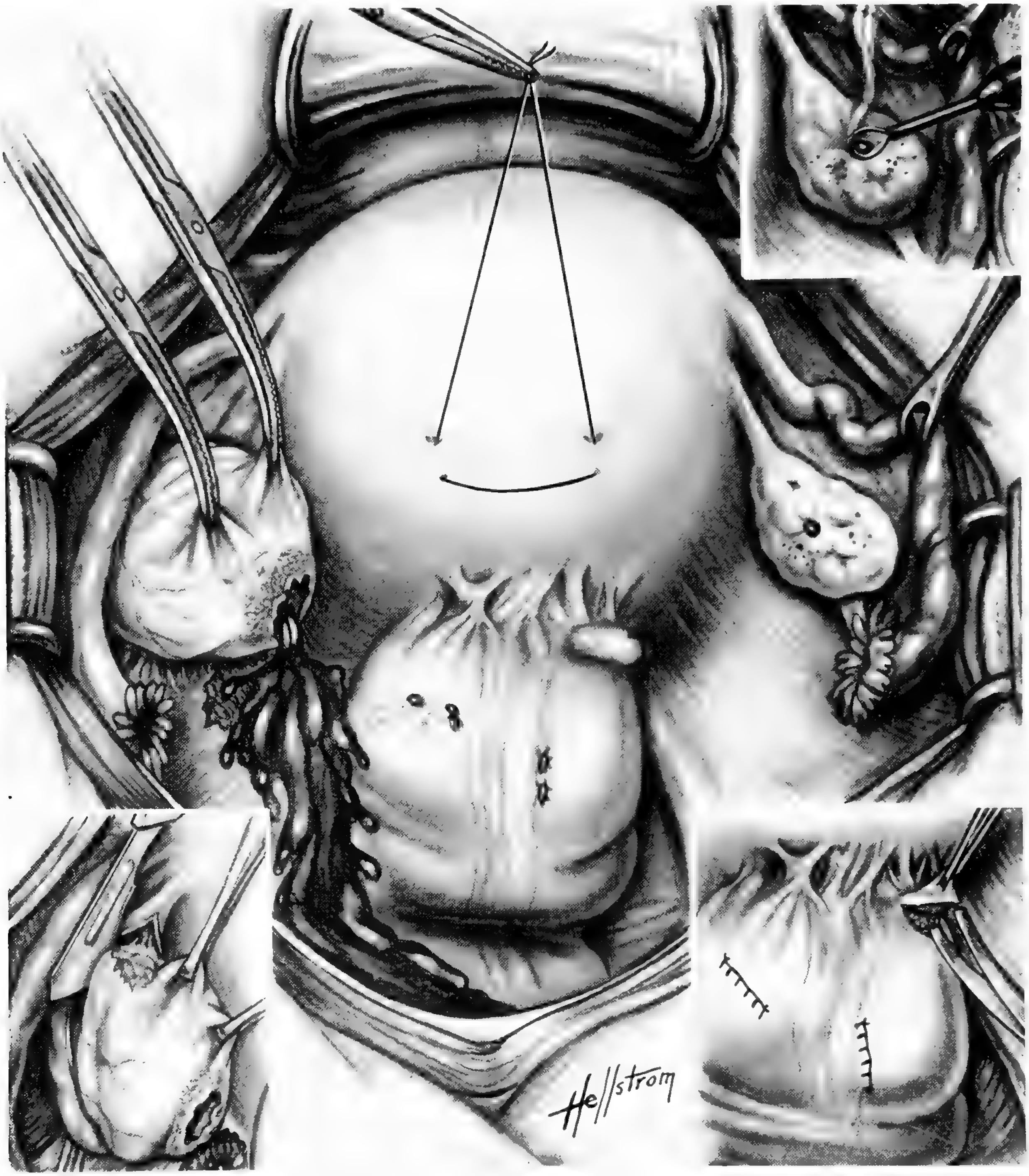


Fig. 273. Conservative operation for endometriosis. The findings indicate an adherent retroversion of the uterus, endometrial cyst of the left ovary, and endometrial implants on the right ovary, in the cul-de-sac and on the sigmoid. After mobilizing the cyst (and almost always spilling the chocolate fluid), the cyst is resected from the ovary. Implants on the right ovary are removed with the electric loop. Those in the cul-de-sac and on the wall of the bowel are excised with scissors.

tion is excised. Evidently the deeper scar tissue may not contain endometrial glands in certain instances.

In cases with severe dysmenorrhea, presacral neurectomy may be performed by making a longitudinal incision in the peritoneum over the promintory of the sacrum, elevating the edges of the peritoneum, and with the Kelly clamp dissecting away the loose areolar tissues that are adherent to the peritoneum, which contain the separated whitish-grey presacral nerve fibers, which spread out over the sacrum and pass down to the uterus and other pelvic structures. The nerves are bunched together in the midline, dissecting as far lateral as possible and using much care not to harm the ureters and blood vessels, after which a portion at least one inch long is excised. The peritoneum is then closed. Another method of neurectomy has been proposed by Doyle, which is the division of the uterosacral ligaments quite deeply as they enter the cervix. They are ligated and brought together behind the cervix, to make it impossible for the nerves to regenerate and extend again into the uterus. Doyle indicates that this procedure will divide most of the pain fibers and that in cases with primary dysmenorrhea the approach through the vagina maybe quite satisfactory.

The excision of the implants in the depth of the pelvis may be followed by marked bleeding. Hot packing, and preferably isolation and ligation of the small blood vessels are to be preferred. Coagulation of small vessels may be satisfactory. Inaccessible areas of endometriosis or those on the back of the cervix may be removed readily with the electric loop, controlling bleeding at the same time. Raw areas are closed over with fine chromic catgut sutures. As a rule the appendix is excised as a routine procedure. A form of suspension of the uterus is to be advised as a rule, although there are exceptions. The modified Gilliam suspension is particularly satisfactory. The round ligaments are drawn through the internal inguinal rings and sutured to the undersurface of the anterior sheath of the rectus muscle with silk. This is described under "Displacements of the Uterus." The conservative operation for endometriosis is a distinctive one, and is performed rather commonly over a period of time, because endometriosis occurs frequently in gynecologic practice. By no means do all require operations, in fact, a minor percentage do, but those who meet the criteria of serious indications for surgery will need this similar procedure not too infrequently.

A semi-conservative operation is that of hysterectomy, with conservation of one or both ovaries, or a portion of ovarian tissue. Actually, this is not conservative at all, because nothing should be considered conservative that does not preserve the child-bearing function. Hysterectomy is necessary, when there are multiple fibroid tumors of the uterus, or obvious and marked enlargement of the uterus as from severe adenomyosis, a diagnosis that is suspected from the severe symptoms of bleeding and pelvic pain. If one or both ovaries can be retained, and if they are reasonably normal, or if the endometriosis within the remaining ovary can be completely extirpated, and if there is not extensive endometriosis remaining in the pelvis, certainly it is proper to leave normal ovarian tissue. If an extensive amount of endometriosis cannot be removed from the depth of the pelvis or the bowel wall, then as a rule the remainder of the ovarian tissue should be removed. It is foolish to become overly sentimental in saving ovarian tissue, when serious symptoms may be anticipated from its retention in the pelvis. A few authors have felt that hysterectomy alone will give good results, although extensive endometriomas and sizeable bilateral endometrial cysts of the ovaries are present. In our experience with a relatively small number of cases that have had hysterectomy without removal of the endometriosis, this has not been the case. It is difficult to understand how severe endometriosis that is symptomatic

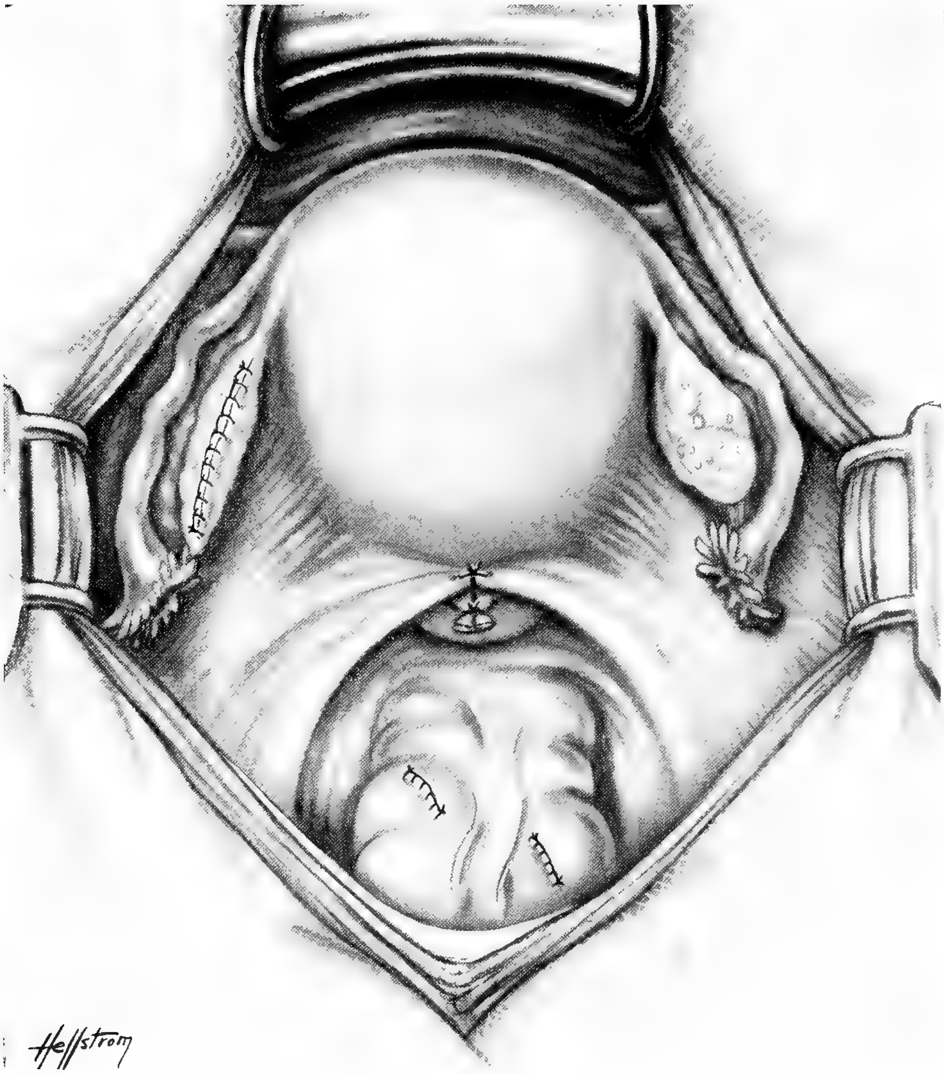


Fig. 274. Conservative operation for endometriosis completed. The left ovary has been resected and sutured over. Implants on the right ovary have been removed with the electric loop. Those in the cul-de-sac and on the bowel wall have been excised. The uterosacral ligaments have been divided (Doyle denervation) and plicated behind the cervix. A modified Gilliam suspension of the uterus completes this procedure.

could be helped after removing only the uterus.

Radical surgery includes the removal of the uterus, and both tubes and ovaries. Unfortunately, this procedure must be performed in a generous proportion of cases, forty per cent, in our experience. From one author to another, the percentage of radical surgery varies greatly, in some instances because the operation has been deferred year after year until finally the patient is incapacitated and the endometriosis has become so involved that only radical surgery can be done; on the other hand, the philosophy of the operator may be such that a radical approach is indicated in the majority of cases. One should have a conservative attitude as far as possible in the saving of the reproductive function. That is the purpose of the female in this life, and if she is not able to fulfill that function, or to have the possibility of doing so, a great void has been produced, and complete failure of the surgeon must be acknowledged. On the other hand, in many instances the percentage of radical surgery will be much smaller because either the patients operated on all have a much earlier stage, if they can be found in this stage, or the operator will bend over backwards and leave in endometriosis, minute nubbins of ovarian tissue, and degrees of pathology in the pelvis with which he feels the patient may live and be reasonably happy. This, again, is a matter of experience, and to some extent, of philosophy. There is a balance between the extremes.

In our experience radical surgery has been performed in forty per cent of patients who have necessary operations. This means that patients with severe bilateral endometrial cysts of the ovary, with sizeable myomas of the uterus and with extensive involvement of the pelvic peritoneum and bowel wall, and particularly when the patient is older than thirty-five years, and especially if she has had children (fortunately fifty per cent of all cases have had children), then radical surgery not only is necessary but may be readily accepted. Extensive surgical procedures can be extremely difficult to carry out in cases with advanced endometriosis. The adhesions involving the bowel, ovary, uterus, peritoneum, omentum, and bladder, may be most difficult to separate and be associated with marked oozing or sharp bleeding. This is particularly true in the mobilization of the endometrial cysts and the separation of the uterus from the rectum. In the excision of the pelvic organs, removal of the cervix may seem extremely difficult, because of the proximity of the rectum when it is adherent by the extremely dense adhesions of endometriosis. Rectovaginal fistula has followed this excision on occasion. If one is most careful to excise through the thickened tissue down to the cervix itself, a plane of cleavage may allow rather ready separation of the rectum from the cervix and vagina. The cervix can be removed as a rule, unless the patient is severely obese, and removal of the cervix is always to be desired because of the ever-present potentiality of carcinoma of the cervix in later life.

In the procedure of total hysterectomy and bilateral salpingo-oophorectomy for extensive endometriosis, there may be marked oozing from many areas in the pelvis, some of which seemingly cannot be completely controlled, in spite of multiple sutures in the peritoneum, of coagulation of bleeders, and hot packs used during the operative procedure. Unfortunately, some oozing may continue into the abdomen after the operation, and pelvic hematomas of small degree may form, which must be slowly absorbed over a period of time. In rare instances, large hematomas may occur which require evacuation.

After the patient has healed from her surgery, that is, six or eight weeks from operation, the vagina has become thin and shows the atrophic changes of the menopause. As a rule, above the apex of the vagina there remains a moderate induration across the pelvis, which is more slowly absorbed over a period of weeks or a few months. In some instances the unexcised endometriosis is so severe in the bowel, bladder, and pelvic peritoneum, that one does not dare give estrogenic hormone in future years. These patients are advised to refrain from any estrogen, at least for a period of years, although estrogen cream may be used in the vagina to prevent dyspareunia and the other symptoms of atrophic vaginitis. If the remaining endometriosis is not too marked, very small doses of oral estrogen may be tried, as conjugated equine estrogens, 0.3 mg. (Premarin) daily for a period of months or years, to prevent the annoying symptoms of the menopause, to keep the patient in the best general physical condition, to prevent the atrophy of the vagina, with its tenderness, soreness, and watery discharge, and even to aid the bones in their calcification and blood vessels in their resiliency. Testosterone in any form over any prolonged period of time is not to be preferred, unless absolutely necessary, that is, unless there is most extensive endometriosis remaining in the pelvis, coupled with symptoms of the menopause so severe that it seems that something must be used, more than sedation.

In the surgical treatment of endometriosis, one always prefers to excise all remaining endometrial implants in the pelvis if possible. This may be carried out in many instances, if great care and sufficient time and extensive dissection are used. If the wall of the bowel is involved in one or more areas, as a rule an effort is made to excise this growth by cutting through the serosa around it and dissecting down to the muscularis and submucosa as far as is necessary, and evidently to remove most of the endometriosis in a considerable percentage of patients. If the involvement has extended well into the lumen of the bowel, though not to ulcerate it as a rule, but to produce a sizeable mass and to cause severe bowel symptoms, then resection of that portion of the bowel wall, even its entire circumference, is to be performed. In these instances intestinal antiseptic preparation for possible bowel surgery is always to be desired. If one has anticipated this and administered sulfasuccidine, sulfaphthalidine and neomycin, the procedure may be carried out with relative impunity. If there has been no intestinal preparation, but if the intestine has had careful preoperative cleansing, then excision is indicated, making every effort to spill no gross fecal material. The bowel is approximated with continuous catgut suture in the mucosa and interrupted silk in the muscularis, the excision being made across the bowel and not longitudinally, to avoid narrowing the lumen. Bowel surgery is followed by routine antibiotics.

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CHAPTER XI

Relaxations and Displacements – Fistulas

Most of the relaxations of the pelvic floor are related to childbirth, and this includes relaxed vaginal outlet, cystocele, rectocele, enterocele, and prolapse or descensus of the uterus. However, the congenital weaknesses are important factors, and may explain why some women have more relaxations than others after childbirth, and of course explains the less frequent similar relaxations with never a pregnancy.

RELAXED VAGINAL OUTLET AND RECTOCELE

The *relaxed vaginal outlet* includes stretching of the orifice with separation and disruption of the small external constricting muscles, and more obviously with separation of the levator muscles. Outlet stretching may be greatly diminished by routine episiotomy at delivery, followed by careful closure of the incision. But, for those many who will deliver spontaneously or rapidly, this relaxation will continue to occur.

Symptoms may include a sense of weakness, inability to lift, and diminished sexual pleasure. Often the symptoms are not definite. In general, perineorrhaphy is one of the most valuable operations in surgery, as measured in increasing the well-being of the patient. This does not mean that all relaxations should be repaired, in fact, it is well accepted that asymptomatic relaxations should be left alone, until such time, if ever, that symptoms do appear.

The separation of the muscles is determined by separating the examining fingers over the posterior margin of the orifice, testing with pressure against the muscles. Also the patient is asked to strain down, as with labor or defecation, and attempt to constrict the vaginal orifice voluntarily. Degrees of weakness become readily obvious.

As a rule, relaxed vaginal outlet is associated with a rectocele, so that perineorrhaphy and posterior colporrhaphy are used synonymously, though strictly speaking they may be different.

The *rectocele*, or bulging of the rectum into the vagina, occurs quite frequently and is classified of slight, moderate, or marked degree. The moderate rectocele has an obvious bulge at the orifice of the vagina, whereas the marked or large rectocele, has the large bulge extending outside the vaginal orifice. The symptoms of weakness in this local area, bearing-down discomfort, and, particularly, difficulty in defecation, may cause much distress. While one patient may have these symptoms in marked degree, the next patient with the same finding may have no complaint. The obvious weakness, with lack of expulsive muscles and large sac of rectum into which the feces accumulate, explains the dyschesia which results, to the point of using the fingers in the vagina to press the rectum back into position. Inspection shows the bulge, but the forefinger in the vagina and middle finger in the rectum demonstrate the thin wall and sac-like form. Some consider this a herniation of the rectum into the vagina in the broad sense, but most will reserve the term hernia for prolapsing sacs of peritoneum. Again, the

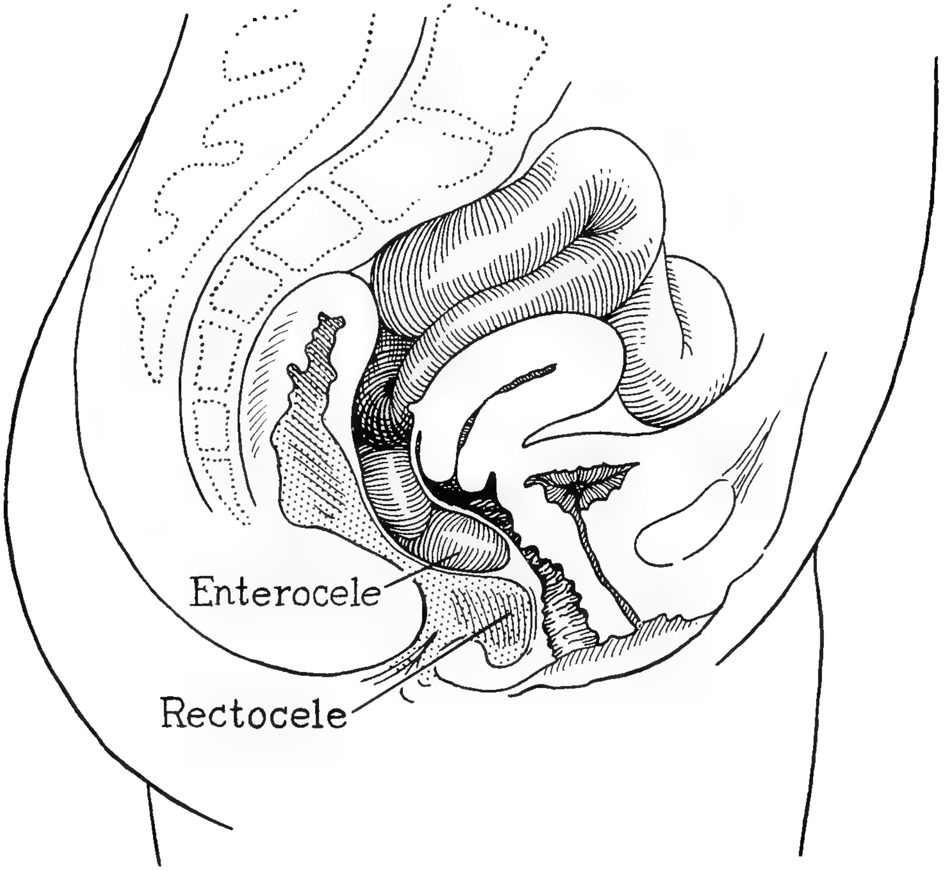

Fig. 275. Enterocele and rectocele. The posterior cul-de-sac has become greatly deepened, due to a congenital weakness in the area. Small intestine falls into the sac. The rectocele shows the weakness over the anterior wall of the rectum, allowing it to bulge into the vagina. Most commonly follows stretching from childbirth, but may be caused by congenital weakness in the area.

indication for operation as a rule is the presence of true symptoms.

Posterior colporrhaphy may be performed with local, spinal or general anesthesia (and even hypnosis), but today most prefer intravenous sodium pentothal, reinforced with nitrous oxide, when necessary. The posterior wall of the vagina is incised in the midline, after undermining the tissues, and this should extend above the bulge of the rectocele, if not to the apex of the vagina. A long continuous lock-stitch of fine chromic suture is placed in the thin, sometimes indefinite fascia over the rectum, extending down to the outlet of the vagina. Then, multiple interrupted sutures are placed in the levator muscles, beginning halfway up the vagina, extending down to the outlet. After excising the excess mucosa, a long continuous lock-stitch of medium chromic suture approximates the mucosa down to the outlet. Finally, the skin of the new perineum is closed with a double layer of fine chromic suture, placed subcutaneously and subcuticularly. There are many variations of this operation.

CYSTOCELE

Drooping of the bladder into the vagina forms a cystocele, which may be classified as of slight, moderate, or marked degree. The moderate cystocele bulges down quite obviously to the outlet, while the marked cystocele comes completely outside, as a large bulge, perhaps the size of a goose egg. As a rule, there is associated relaxed vaginal outlet and rectocele. Also degrees of prolapse of the uterus usually occur. But, sometimes the perineal floor is quite firm, and the cervix may not descend abnormally, and yet a large cystocele may be present. This is particularly true as a late postoperative recurrence.

The symptoms are weakness, bearing down, pressure, and often inability to empty the bladder. At times, the patient must press the bladder back into the vagina to be able to void, and not infrequently to be able to empty it. The residual urine may cause pressure discomfort, and often is associated with chronic cystitis, with its symptoms of frequency of urination, pain, and burning. In fact, the frequency is a prominent symptom, and may be associated with residual urine, without infection. The feeling of pressure from the position of the bladder may cause some of the frequency by bringing it to mind, because frequency may be absent in the recumbant position at night.

The diagnosis is obvious on inspection, the bulge being more marked with straining. The two fingers in the vagina separate the introitus, to visualize the cystocele. Examination in the standing position, the position that causes the symptoms, with two fingers in the vagina shows the extent of the bladder prolapse more clearly, and may show other prolapse of the uterus and rectum, not realized from examination in the dorsal position.

If the symptoms are clear, surgery may be advisable. An incision from urethral meatus to the cervix separates the vaginal mucosa, which is then separated from the fascia under the bladder. The fascia is plicated with interrupted chromic suture. An extra suture or two are used to elevate the bladder neck, to produce an angle (to be mentioned in more detail later). The excess mucosa is trimmed away, and the vagina is approximated in the midline with interrupted suture.

Some patients with marked symptoms do not wish to have surgical correction, a very few seem too old to the surgeon, and a few are poor risks because of medical diseases, such as cardiovascular renal disease and diabetes. For these, various pessaries are used. The Gelhorn pessary and its modifications are the most useful. The Smith and Hodge pessaries do not hold the bladder up very well. The larger hard ring pessary may be helpful at times. The soft rubber, air-containing doughnut is useful at times. The Bell pessary of cuboidal sponge rubber with semispherical indentations in the sides is ingenious. The old Menge pessary of hard rubber, a round ring with detachable nob extending down from the center crossbar, is useful. Most of these pessaries are used more for prolapse of the uterus with associated cystocele and rectocele, but at times the cystocele alone is the problem.

A main difficulty with these pessaries is the irritating effect on the vaginal mucosa. A point of any undue pressure develops ulceration and granulation tissue. All of these pessaries should be removed at intervals of six to eight weeks, be washed thoroughly, and the vagina should be inspected. If there is no irritation the pessary may be reinserted. After observation on several occasions, the pessary may be left in place longer periods of time. Soft rubber, as in the doughnut pessary and the Bell foam rubber pessary, produces irritation quickly and is not too desirable in the vagina. Postmenopausal vaginas are aided by thickening with estrogenic hormones. One would always prefer surgical repair, but sometimes it is not acceptable or practical.

Cystocele repair is not always successful, or at least, recurrence does occur. With large cystocele, some degree of recurrence follows in probably thirty to forty per cent, though to a bothering degree in only a minor percent. Surgeons may quickly deny this recurrence rate, but that may depend on how critically their cases are followed.

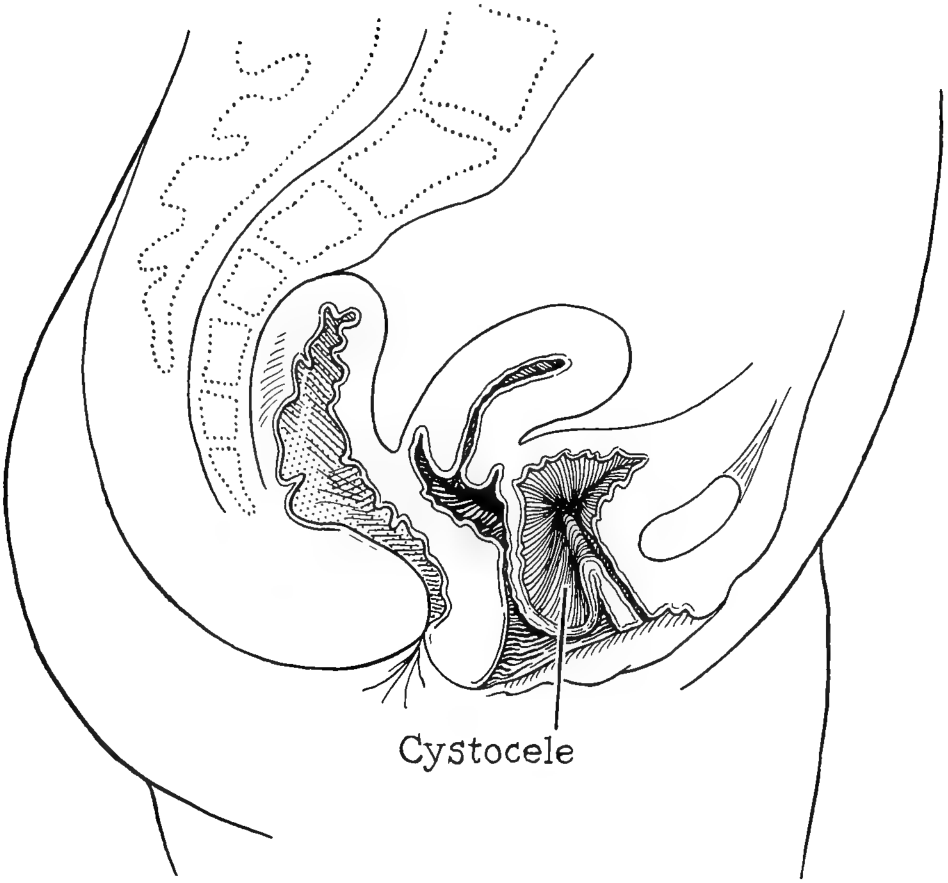

Fig. 276. Cystocele. The fascia and muscle beneath the bladder have been greatly stretched or weakened, allowing the base of the bladder to fall into the vaginal area. A relaxed vaginal outlet from disruption of the outlet muscles is also demonstrated.

PROLAPSE OF THE UTERUS

First degree, second degree, third degree prolapse, and procidentia

First degree prolapse means that the cervix has dropped part of the way toward the oriface of the vagina. Second degree prolapse, or second degree descensus, means that the cervix is at the level of the outlet of the vagina. Third degree prolapse means that the cervix is outside of the vagina. This, of course, may be to a slight extent or to a severe degree. When the uterus is completely outside the introitus with inversion of the vagina, the condition is called procidentia. Sometimes, observers have called third degree prolapse, with the cervix outside the orifice, procidentia, but it seems better to reserve the latter term for the inversion of the vagina with complete prolapse.

The etiology of prolapse is, for the most part, childbirth, but in some cases it is congenital, or at least develops on a congenital basis in later life. It is obvious that the process of delivery of the fetus at term not only stretches the diameter of the cervix to ten or twelve cm., or more, but also in the process of bearing down with the expulsive, contracting forces of the uterus, the supporting cardinal ligaments and the uterosacral ligaments are stretched greatly. As the fetal head and shoulders pass through the vagina, the levator muscles and the urogenital diaphragm, with its fascias and lighter muscles,

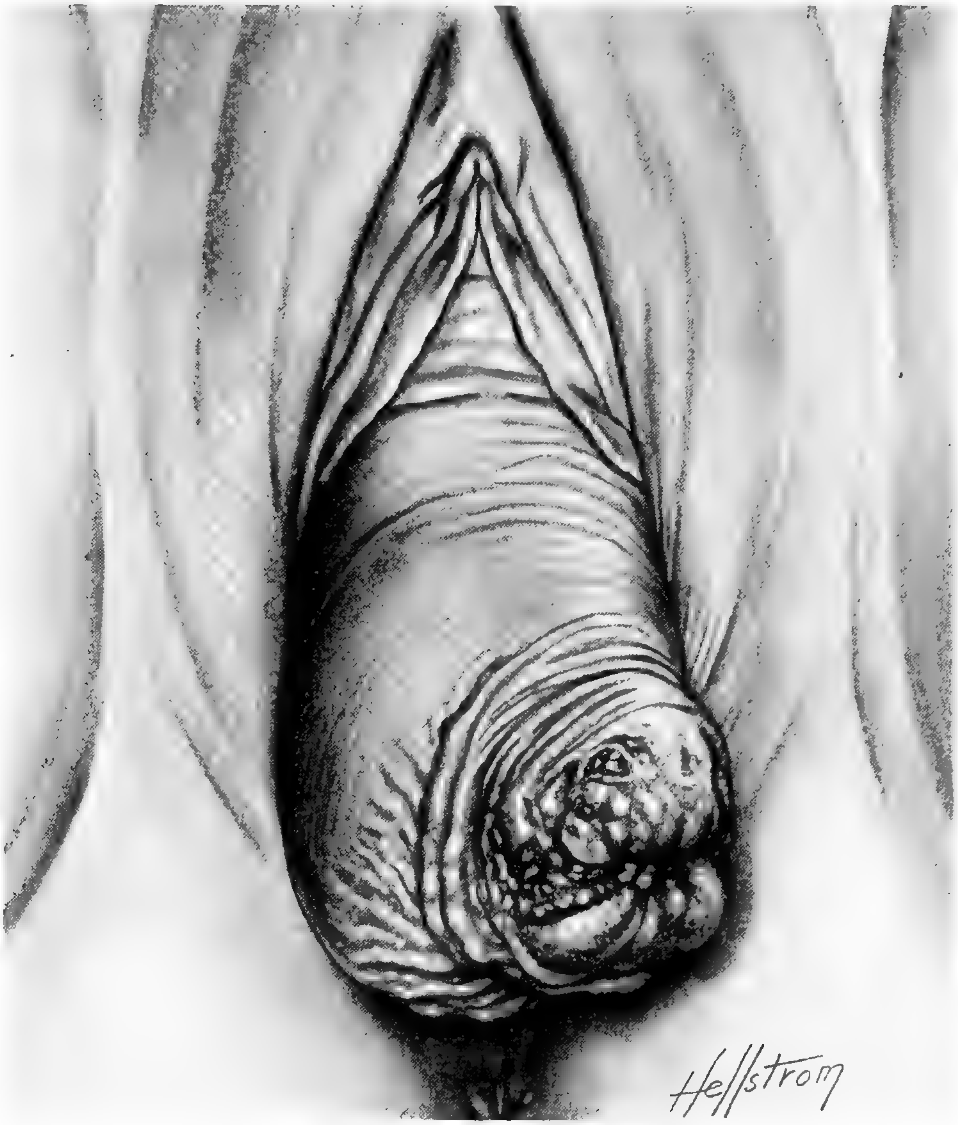

Fig. 277. Complete prolapse, procidentia, inversion of vagina. In contrast to third degree prolapse in which the cervix, not the corpus necessarily, protrudes outside the vaginal outlet. The vaginal walls become thick and cornified from exposure to the air and friction. The cervix has developed a moderate "erosion" and chronic infection from external contacts.

are stretched markedly to allow the fetus to come through the opening. In the majority of young women after delivery, a remarkable contraction returns these structures almost to the normal, the elasticity of the muscles and ligaments snapping them back into position; yet, as the years pass the original stretching at the time of delivery may allow the uterus and the vaginal wall gradually to relax more and allow degrees of prolapse, as a rule associated with cystocele and rectocele and, at times, enterocele. With more numerous deliveries, the degree of prolapse is often more severe, but this is not always true. Occasionally, a woman may have had a number of children, and yet have relatively little prolapse and relaxation, whereas another patient with only one child may have severe degrees of cystocele, rectocele, and third degree prolapse. Prolonged labor and difficult delivery may well be factors in the development of prolapse, though, again this is not always necessary. The properly performed episiotomy and its proper repair immediately after delivery must preserve the pelvic floor in a large percentage of women far better than those who have delivery without episiotomy. That the episiotomy and repair may prevent the development of prolapse of the uterus is not so clear, but perhaps the outlet muscles are important even in descensus of the uterus.

Not too infrequently one sees degrees of cystocele and rectocele, and prolapse of the uterus, particularly the latter, in nulliparous women, or unmarried women. At times, the uterus is completely outside the vagina. Obviously over-stretching of ligaments could not cause this descensus, and evidently there must have been an unusual degree of weakness in the supporting ligaments and muscles. X-ray films of the spine in these cases frequently reveal the occult spina bifida, which apparently has some association or causal relation to the nerve weakness that may be responsible for the loss of tone in the muscles and ligaments and allow prolapse to occur. In spite of the finding of occult spina bifida, it remains a curiosity because no other treatment can be done other than surgical repair, although one must realize that recurrence of the prolapse may follow because, obviously, the tissues must be weaker than the normal.

The diagnosis of prolapse of the uterus most often is made by the patient herself, who states that the neck of the womb has dropped to the outlet, or outside the vagina, because she has felt it and has seen it with the mirror. Lesser degrees of prolapse, that is, the first degree prolapse, obviously cannot be determined by the patient herself, unless she notices it in inserting the diaphragm or douche nozzle. The symptoms of prolapse are primarily bearing down, pressure sensations deep in the pelvis, a feeling that the insides of her abdomen will fall out through her vaginal orifice, associated with degrees of some low backache, which by itself is not a characteristic symptom, often with dyspareunia, and often with disturbance of menstrual function, if the patient is in menstrual life. These symptoms may be mild, or may be most severe and disabling. The conclusive diagnosis is made by pelvic examination, in which the cervix is seen at the outlet of the vagina, or outside the vulva, in the second and third degree prolapse. With the first degree prolapse, one notes that when the patient strains, the cervix, usually with the bladder and rectum, bulge down into the vagina in varying degree. As a rule, when there is any question of prolapse or in the face of the previously mentioned symptoms, one will attach the tenaculum to the cervix and pull gently or moderately to see how far the cervix will descend. Also, as a rule, at the conclusion of the complete pelvic examination, the patient is examined in the standing position with her legs somewhat apart, placing two fingers in the vagina to feel the bulging of the vaginal walls and the descent of the cervix. This is especially noticed as the patient strains. It is in this position that most of the symptoms occur that are related to prolapse, and it is important to palpate the vagina and cervix in this symptomatic position.

The treatment of genital prolapse, as a rule, depends on the symptoms associated with it. If there are no symptoms in first or second degree prolapse with a related cystocele and rectocele, the latter present as a rule in degree, then no treatment is advised. If the symptoms of bearing down and pressure are relatively mild, the knee-chest position may aid in helping circulation, in restoring the normal position of the uterus, at least for a short period of time, and be sufficient to relieve the symptoms that are of little import anyway. The Kegel exercises of constriction of the levator and vaginal muscles, the so-called pubococcygeal muscles, not only aid in improvement in stress incontinence but also may aid in the degree of prolapse to some extent (this latter point is not so clear). In young women in the childbearing age,

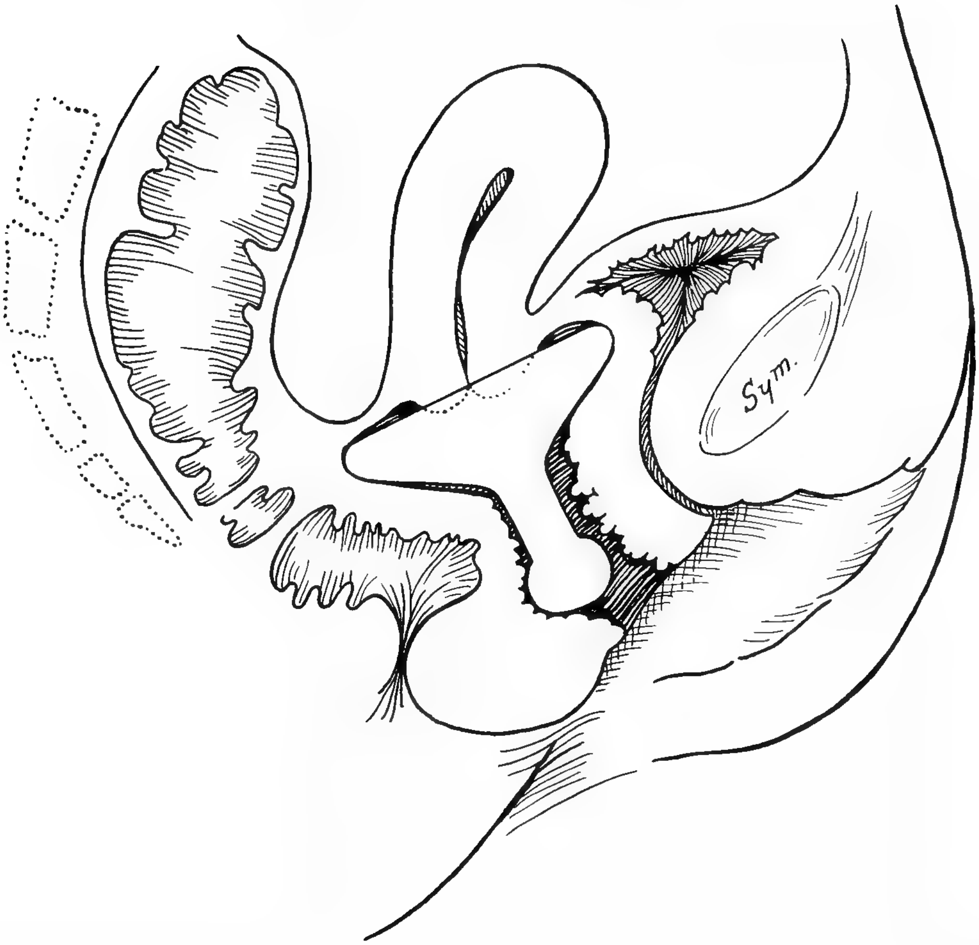

Fig. 278. Prolapse of the uterus and cystocele supported by the Gelhorn pessary. This may be very helpful in the treatment of the elderly, infirm, or the patient who fears surgical correction.

they should be allowed to continue their fertility. Particularly for women who may desire more children, the Smith or Hodge pessary may be inserted, to be changed at intervals of six or eight weeks, observing the vagina for ulceration and irritation; the pessary may give complete symptomatic relief of the minor degrees of prolapse. Similarly, in the elderly woman, who is not a good surgical risk, or fears surgical procedures intensely, similar pessaries may be used, to be changed at regular intervals. While the Smith and Hodge pessaries may be satisfactory, the large ring pessary or the doughnut type of soft rubbery pessary containing air in its center may be used, though the soft rubber is much more irritating than plastic materials. More often if pessaries are to be used in the elderly patient, some form or variation of the Gelhorn pessary is to be preferred, as it gives more satisfactory results in supporting the cervix. The use of this pessary, as with all pessaries, depends on a reasonably satisfactory perineal outlet support. If the perineum is completely relaxed, the pessary cannot be expected to be maintained in place satisfactorily. The use of pessaries may be continued as long as desired in the young patient, and as long as necessary in the elderly patient who does not want an operation. Certainly, one must watch carefully for irritation from all pessaries, because they may produce degrees of mechanical vaginitis from rubbing the walls of the vagina, or even rather severe ulcerations. If forgotten and left in the vagina for prolonged periods of time, the pessary may become embedded within the vaginal mucosa and be removed only by surgical excision through the vagina.

Surgical operation is the preferable treatment, whether the patient be young or old, if the symptoms are disabling. An exception, of course, is the young patient who wishes more children in the immediate future, and she may have the use of pessaries and be encouraged to complete her family, after which definitive therapy may be undertaken.

There are some four basic operative procedures that may be used for the treatment of prolapse of the uterus. In the young woman who has had several children, but may not have completed her family, but who does not wish to have more children in the next few years, who has marked symptoms from prolapse, cystocele and rectocele, usually the latter two being present though not neces-

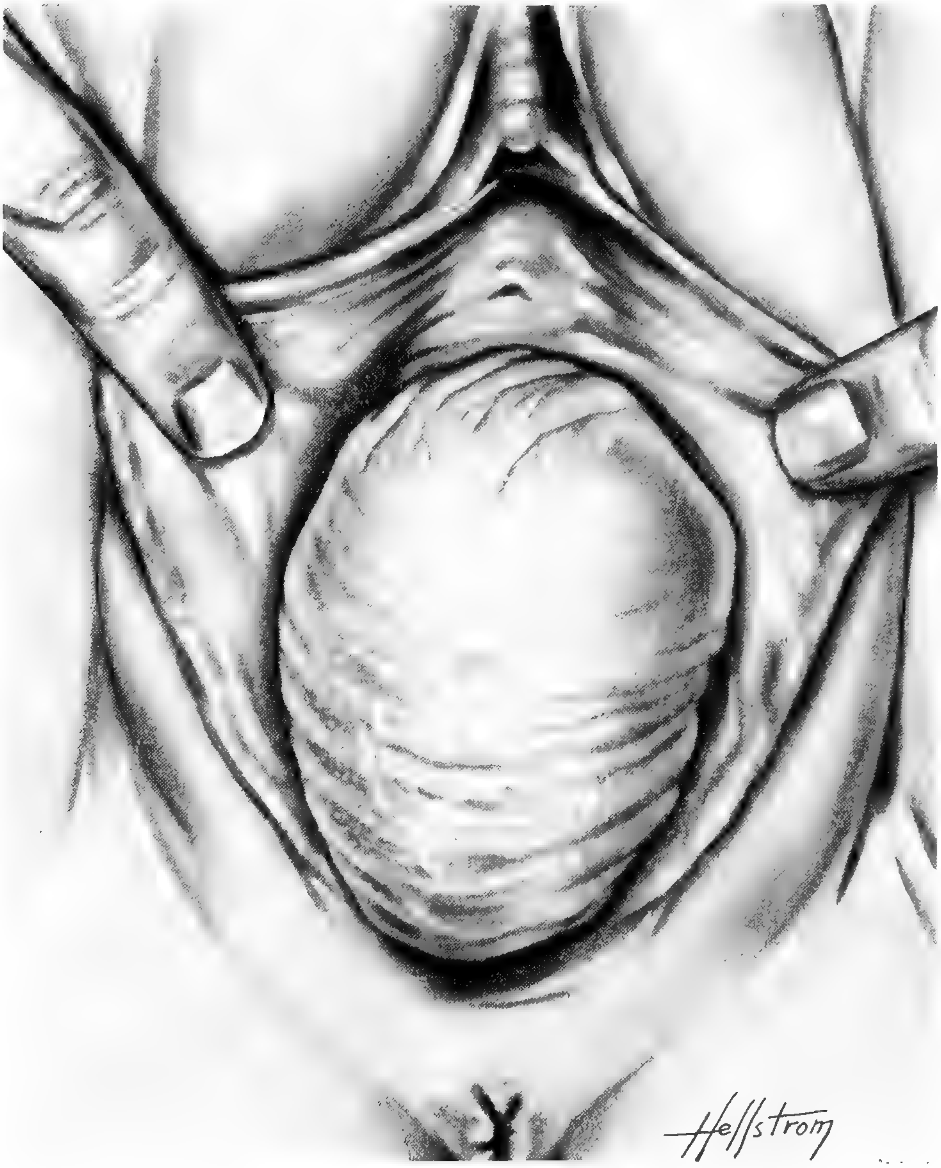

Fig. 279. Large enterocele. This huge protruding mass arises between the cervix and rectum and is filled with small intestine. It extends quite outside the introitus.

sarily so, then a conservative operation may be performed with good results. This involves the cystocele and rectocele repair from below, then an abdominal incision with suspension of the uterus by any of the many different methods, which are discussed under the next section on uterine displacements, along with particular effort to shorten the uterosacral ligaments in order to draw the cervix back up into the pelvic cavity. Such an operation, if performed carefully, may give most satisfactory results, and yet retain fertility, over a period of many years. With subsequent pregnancy, there may be recurrence of the cystocele, rectocele, and prolapse, or retroversion, but this is a matter of concern no more than in the normal nulliparous patient who desires to have a child. That relaxation, displacements, and prolapses do occur in the normal patient is not a deterent to pregnancy and delivery. Some obstetricians may prefer a Caesarian section after cystocele and rectocele repair, but that is not truly necessary as a rule, though it is a matter for individual decision. The second operation used for prolapse is the Manchester-Fothergill operation. This is the performance of a cystocele and rectocele repair with amputation of the cervix and suturing of the cervical ligaments, also called the cardinal ligaments, in front of the cervix. This acts as a deterent to subsequent prolapse of the uterus, and may give a satisfactory suspension of a prolapsed uterus. However, there are degrees of recurrence after this procedure, and it has long been felt that the usefulness of these uteri for further pregnancies is probably impaired by the cervical amputation. It appears that sterility is much higher after this operation. The recent studies in incompetency of the cervical os causing late miscarriage due to disruption or loss of the sphincter muscle fibers in the cervix may be applicable to the uterus involved in the Manchester-Fothergill operation. This operation has been used for many years in the British Isles as the prime treatment for prolapse. That situation in England, though, has changed materially in the past few years, and vaginal hysterectomy has been accepted more widely at this time. The third operation that may be used for prolapse is the Spaulding-Richardson operation, which goes further than the Manchester-Fothergill procedure, in that not only is the cervix amputated but also the corpus of the uterus is excised after drawing it beneath the bladder flap into the vagina, and there is left a "keystone" of lower uterine segment in place after the excision of the corpus and of the cervix itself. It is felt by adherents of this operative procedure that the maintenance of this keystone in the apex of the pelvis allows one to suture the pubocervical fascia, and the cardinal ligaments, into this portion of the cervix and allow a far better suspension of the pelvic floor. Because this operative procedure may be more difficult than the vaginal hysterectomy, and because it leaves a portion of uterus that may develop further difficulties, whether from bleeding or from tumor formation as a possible complication in later years, this procedure has not been widely accepted.

The most popular treatment at this time in this country, and probably in most places abroad, for prolapse of the uterus is vaginal hysterectomy with proper repair work as indicated. This frequently used operation, while first performed successfully in 1818 by Langenbeck, received its rejuvenation by Heaney in 1932-36 in Chicago. He pointed out the virtues of the operation, not only for prolapse of the uterus but for varying reasons for hysterectomy. There are many different variations for the performance of this operation, and several drawings are shown to demonstrate one method in this book (Figs. 164-185). This type of surgery does require careful selection of the patient, care in its performance, and requires many sutures, each of which has a particular purpose. As one learns a vaginal hysterectomy technique well, one's enthusiasm for the operation rises continuously.

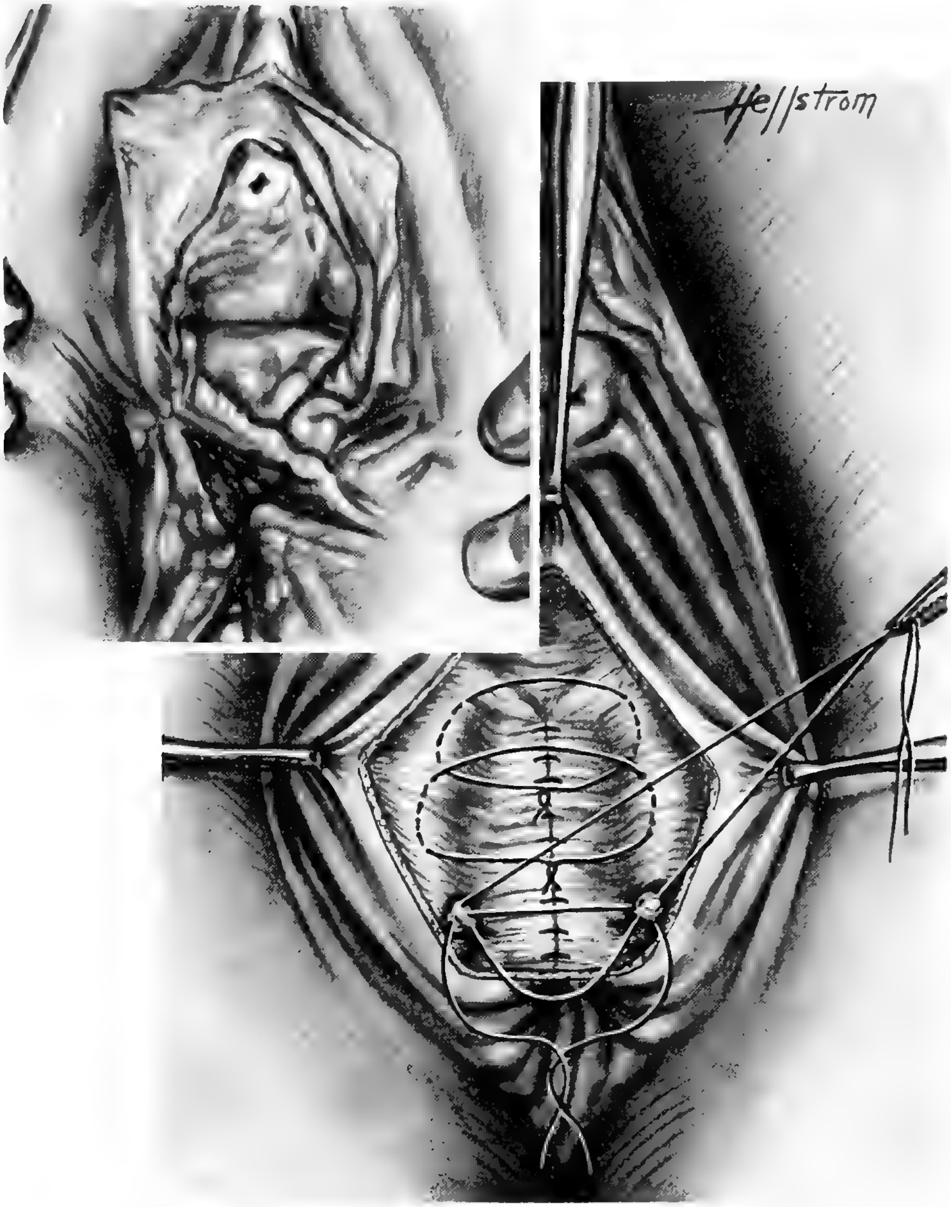

Fig. 280. Third degree perineal laceration. The sphincter was completely divided years ago, and the patient is largely incontinent, except for some benefit from her constipating regime. In the repair, all scar tissue is excised, and closure is made in anatomic layers. The bowel has had antiseptic preparation. Of great importance is incision through the sphincter posteriorly (at six o'clock) at the conclusion of the operation. This prevents any gas pressure against the suture line. Later, healing is followed by formation of an intact sphincter.

INCONTINENCE OF URINE

Incontinence means loss of control, and when applied to the urinary bladder means loss of control or maintenance of urine in the bladder. Complete incontinence is seen in rare instances, usually with extensive tears into the internal urethral sphincter or with fistula formations, and in other rare occasions, apparently is related to neurological disease. On the other hand, stress incontinence occurs extremely frequently. This means the loss of urine, whether in small amount or in larger amounts, after lifting, straining, walking, running, coughing, sneezing, or other possible exercises that may cause increased pressure on the bladder and urethra. In the patient with incontinence, whether partial or complete, one always studies the case carefully for possible fistulas, particularly for an extra ureter which may open into the vagina or into the vestibule or into the urethra itself, allowing urine to be secreted continuously from the extra opening. One looks for overflow incontinence, because in the neurological bladder there is a paralysis of the bladder muscle, whether it comes from transection of the spinal cord, from severe injury to the cord, or from destruction from tabes dorsalis (syphilis), or other neurological diseases. With overflow incontinence, one finds the bladder distended and on catherization a large amount of urine is obtained. Recently, it has been suggested that the cliteroanal reflex may be used to determine the normal reflexes and intact pathways of nerve control from the sacral nerves. In this reflex, one pinches the clitoris while using the tip of the finger of the other hand in the anus. Squeezing the clitoris causes the anal muscles to contract involuntarily, and causes some contraction of the bulbocavernosus muscle, but this is so slight that it may not be determined in all patients. Spinal cord tumors, multiple sclerosis, poliomyelitis, etc., may be factors in the neurological bladder. Cystoscopy with inspection of the bladder, pyelograms to determine hydroureter and hydronephrosis, cystograms to determine backflow of urine from the bladder into the ureters, and cystometric studies are especially indicated when neurological disease is suspected. Varying amounts of water are placed into the bladder, the patient urged to bear down and strain, and the degrees of pressure that result inside the bladder are recorded on the manometer. With the normal bladder, when the volume of fluid within the bladder exceeds four-hundred-and-fifty or five-hundred cc., the pressure rises rather high, and there is the intense desire to void. This is not present with the neurological bladder.

Stress incontinence of varying degree is quite frequent, mainly follows childbirth some years later, and is associated with cystocele, rectocele, and perhaps of prolapse of the uterus. On the other hand, a recent survey of college girls showed that some degree of stress incontinence from coughing, sneezing, straining, occurs in a large percentage of normal young women, who have never had children, and in whom there is no reason to suspect particular vesical pathology. Degrees of stress incontinence appear extraordinarily frequent, and only the more serious ones are considered necessary for treatment.

Stress incontinence is to be distinguished from urgency incontinence, in which the patient has the feeling of an intense desire to void when only small amounts of urine may accumulate in the bladder, and the desire is so strong that the patient cannot delay and consequently leaks urine, perhaps even continuously. Urgency incontinence, as a rule, is caused by irritation within the bladder, cystitis, trigonitis, or urethritis, and requires treatment of the urinary tract inflammation.

While the most important cause of stress incontinence is parturition, evidently due to stretching the muscles and ligaments that maintain the urethra in its proper position and perhaps that maintain the strength of its muscle contraction, the origin of the condition may be caused by congenital or neurological defects, and in some cases without previous deliveries by unknown reasons. Undoubtedly, a psychogenic factor may be important in some cases, certain women being so nervous that their tension does not allow them to maintain proper contraction of the internal sphincter of the bladder and urethra.

The cause of stress incontinence, if we have ruled out the neurologic and psychogenic factors and separated it from the urgency incontinence, was thought for very many years to be related to a relaxed vesical sphincter, the muscle of the internal sphincter of the urethra and bladder not having sufficient strength to maintain its closure, being disrupted by childbirth in the stretching and tearing of the ligaments and muscles to allow a weakness and incompetency of its action. Consequently, some sixty years ago, Howard A. Kelly devised the so-called Kelly stitch, in which the anterior vaginal wall is reflected from the midline over the neck of the bladder, and this area is isolated and plicated with three non-absorable sutures, usually of silk or linen. This procedure, often accompanied with cystocele and rectocele repair, gave good results in seventy-five or eight-five per cent of cases. The good results were attributed to the reduction of the size of the opening of the urethra and the plicating of the muscle to increase its contractile power.

Jeffcoate, followed by Hodgkinson and others, have pointed out that stress incontinence, or incontinence in general as a rule, is associated with loss of the posterior angle between the base of the bladder and urethra. In order for a woman to have complete continence of urine, it was shown by roentgenograms that the internal sphincter, or neck of the bladder, must be elevated higher than the base of the bladder and the urethra itself, so that there must be present a particular and obvious angle between the urethra and the base of the bladder. In cases of incontinence the sphincter, or neck of the bladder, has dropped down to a level with the urethra and base of the bladder, so that there is no angle. This explanation seems the best one today, although there are some circumstances of incontinence which seemingly cannot be explained in this simple manner. At any rate, now it is felt that the value of the Kelly stitch, of plicating the internal sphincter or neck of the bladder, lies mainly in elevating this area more than tightening it, or reducing its caliber. Since this is understood, in the cystocele repair, one tries not to raise the base of the bladder quite so high as to be on the same level as that of the sphincter, a very slight dropping behind the sphincter being preferable for good continence. Incontinence may follow a cystocele repair, which seems to be a superb repair with a perfectly straight line vagina. Evidently, this straight line is not to be desired for proper function of the bladder.

Other methods of correcting stress incontinence have been available for a longer period of time than this explanation of Jeffcoate, particularly in the use of the strap operations. The Goebel-Frankenheim-Steckel operation utilized a portion of the sheath of the rectus obtained from a longitudinal incision in the abdominal wall, mobilized but left attached at the symphysis, which was drawn down and around the urethra and pulled back up to suture into the fascia of the rectus muscle. For a long time, it was thought that leaving some muscle attached to the strap was necessary and that muscular activity of the abdominal wall would aid in cure of incontinence after this procedure. Now it appears that the effect of the strap is from elevating the bladder neck to produce an angle. In more recent times, Aldridge developed a modification, in which he mobilized straps of fascia obtained by transverse incisions, drew them beneath the urethra, and sutured them together through a vaginal incision, maintaining a proper amount of tightening of the fascia. Millen, of England, developed a similar fascial sling, in which he brought the strips of fascia from the anterior abdominal wall beneath the rectus muscle laterally on each side, and sutured them beneath the urethra, approaching this entirely through the space of Retzius. This procedure is somewhat difficult, and not advantageous over the others. Many different forms of synthetics, or prepared fascias, have been used in these suspension operations. In 1948, Marshall and Marchetti published a method of suturing the pubo-cervical fascia to the sides of the urethra into the periosteum of the symphysis pubis. Earlier they sutured the entire length of the urethra as far as possible, and even the bladder itself, into the symphysis and rectus sheath. Now, elevating the angle of the bladder neck alone, apparently is the important point, and this operation is a rather popular one. When it is performed with ease, without too much bleeding from the bladder veins, and when the periosteal tissues are sufficiently strong to hold the suture without difficulty, the operation seems very satisfactory. When there is profuse bleeding from the bladder veins, and particularly when the periosteum is thin and will not hold a suture, the procedure may be disappointing.

The results of the various methods for the treatment of stress incontinence, or complete incontinence of urine, are not perfect with any method. At times one sees a patient who has had one or two operations performed by the vaginal route with the use of the Kelly suture, and a strap operation, and even has had the Marshall-Marchetti procedure, and still has stress incontinence. Fortunately, these are not frequent in occurrence, but they illustrate the point that the results are not always perfect.

Some discussion of the Kegel method and his perineometer is pertinent. A few years ago, the Los Angeles County Medical Society presented to Kegel a gold medal for having developed his method of teaching a patient constricting vaginal exercises to relieve stress incontinence. In order to aid this method, he developed an elongated rubber balloon, with a manometer attached by a rubber tube, which the patient may use to see the strength of her own contractions as she practices the method, and to see obvious improvement. There is no doubt but the vaginal muscles, the levator muscles and so-called pubococcygeal muscles, which are a part of the complicated levator muscles, are greatly strengthened by contractile exercises. This is a conscious contraction of the vagina, performed by contracting the anus, and drawing the anus and vagina up into the pelvis as strongly as possible, repeated thirty or forty times daily over a period of several months. Kegel and his supporters have believed that ninety-five percent, more or less, of cases with stress incontinence may be cured with this method. Perhaps it is due to insufficient training of the patient in the method of the exercises, or to her lack of pursuing the method, which requires considerable effort and time, that most gynecologists probably are disappointed with this treatment. Among different schools and physicians, the method undoubtedly has varying curative values, and it should be pursued.

MALPOSITIONS OF THE UTERUS

A discussion of malpositions of the uterus includes the aforementioned prolapses of the uterus. Here are included the anterior and posterior displacements of the uterus.

Acute Anteflexion

Acute anteflexion of the uterus is the marked angulation of the corpus of the uterus on the cervix in an anterior position. Some degree of angulation is very frequent and entirely normal. More marked acute angulation of the cervix and the corpus of the uterus may produce symptoms and be of some clinical importance. Rarely one might think the antiflexed uterus could cause bladder symptoms, but it is doubtful that this is ever the case.

The chief symptom associated with acute anteflexion of the uterus is dysmenorrhea. This dysmenorrhea may be very severe and incapacitating. That some of this dysmenorrhea is related to the more-or-less normal functional cramping of the woman before the age of twenty-five years is undoubtedly true, but it does seem exaggerated in some instances where the anteflexion is marked.

As a rule, the anteflexed uterus is smaller than normal. Degrees of hypoplasia of the uterus are so frequent as to be expected; particularly the uterus may be narrow in the

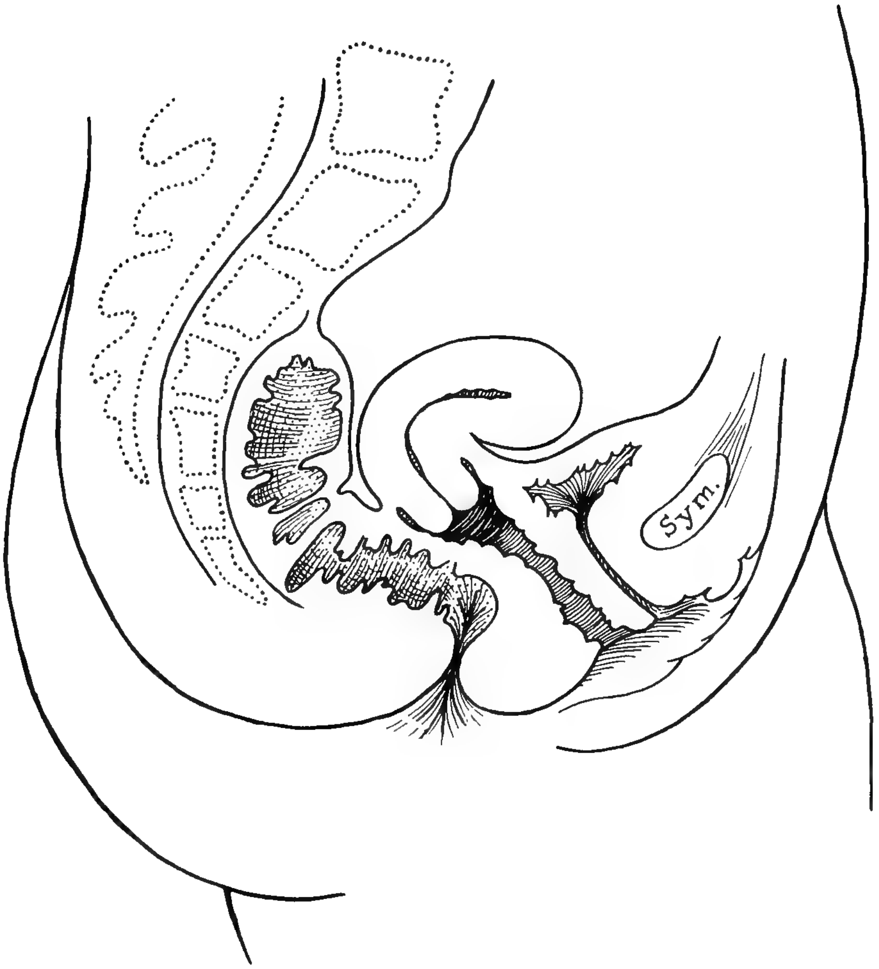

Fig. 281. Acute anteflexion of the uterus. A congenital change of the uterine form, quite frequently occurring, associated, with dysmenorrhea in many, but not all.

fundus. This suggests hypo-ovarinism, hypo-estrogenism, and often hypo-thyroidism.

Occasionally, acute anteflexion is produced by an oversuspension of the uterus, at times the corpus being drawn very far anteriorly. This is not frequent.

The treatment of acute anteflexion is none, unless there are severe symptoms. When the uterus is quite small, small doses of estrogen may be given over a long period of time, hoping there may be some increase in the size of the uterus. Also, when the uterus is quite small with anteflexion, if there is any suggestion of clinical or subclinical hypothyroidism, thyroid extract is prescribed. Pregnancy, naturally, would be a good treatment, enlarging the uterus, stretching the body of the cervix, and often correcting the acute anteflexion. At times, and not infrequently, the acute anteflexion may be associated with sterility. By no means, are all individuals sterile who have hypoplasia or acute anteflexion of the uterus. In a small percentage of individuals with acute anteflexion, the operative procedure of dilatation of the cervix and insertion of the stem pessary may be advisable. Certainly this is reserved for a minority group, which require the insertion of such a pessary. This plastic, straight pessary is sutured into the cervix and left in place for six weeks, after which the sutures are clipped and the pessary is removed simply. There is always some recurrence of the acute anteflexion, sometimes to as severe a degree as originally after a period of time; on the other hand, often these cases may be relieved of their dysmenorrhea, at least for a considerable time. Also, sometimes sterility is relieved after this procedure, if other findings are normal.

Retrodisplacements

Retrodisplacements of the uterus include retroversion, retrocession, and retroflexion. Retroversion is the most frequent form of retrodisplacement, which means that the uterus has turned on its axis, so that the cervix points toward the symphysis while the corpus lies in the cul-de-sac. In some instances, the entire uterus and cervix seem to sag back into the hollow of the sacrum, and this is called retrocession, and while the first degree retrocession is frequent, complete or third degree retrocession is uncommon. Finally, retroflexion with its sharp posterior angulation of the corpus of the uterus on the cervix (the latter in its normal axis) is rather uncommon. It, too, may be associated with dysmenorrhea, as is the acute anteflexion. In reference to retrodisplacement, probably one means retroversion of the uterus in seventy percent of the cases.

The causes of retrodisplacement are congenital in the majority. In fact, between twenty and thirty percent of all women have a retrodisplacement of the uterus. Most of these individuals apparently are born with

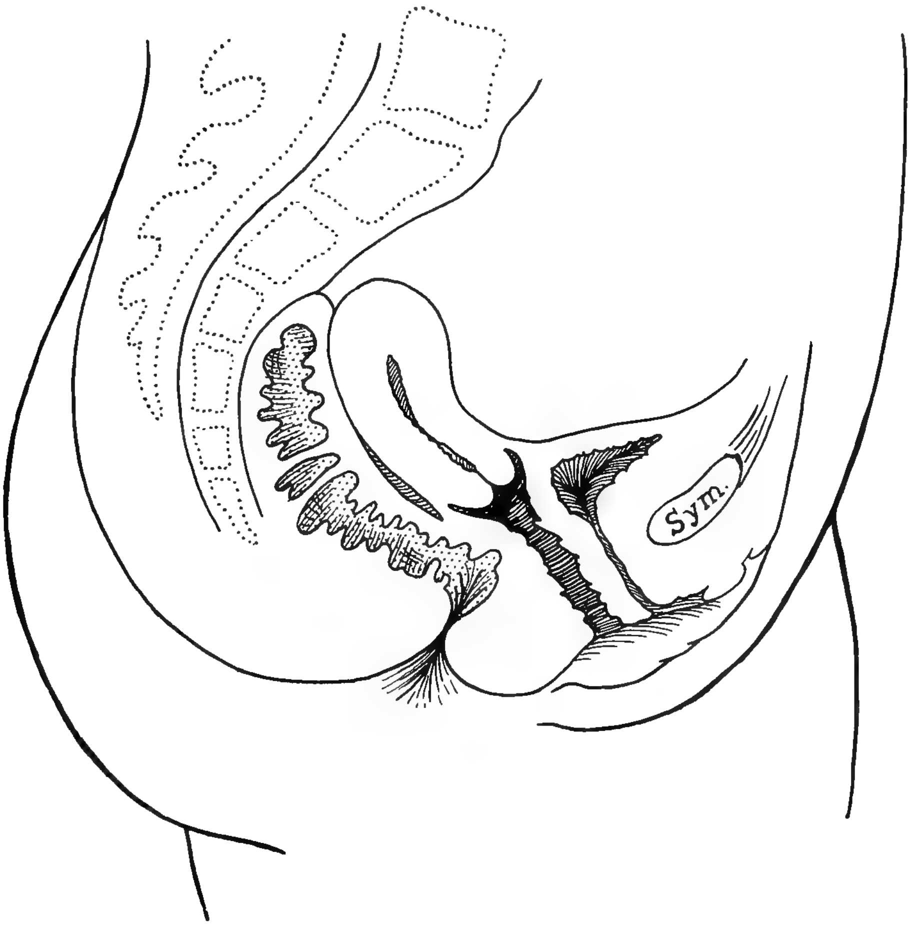

Fig. 282. Retrocession of the uterus. The uterus sags back into the hollow of the sacrum, usually carrying the cervix back also.

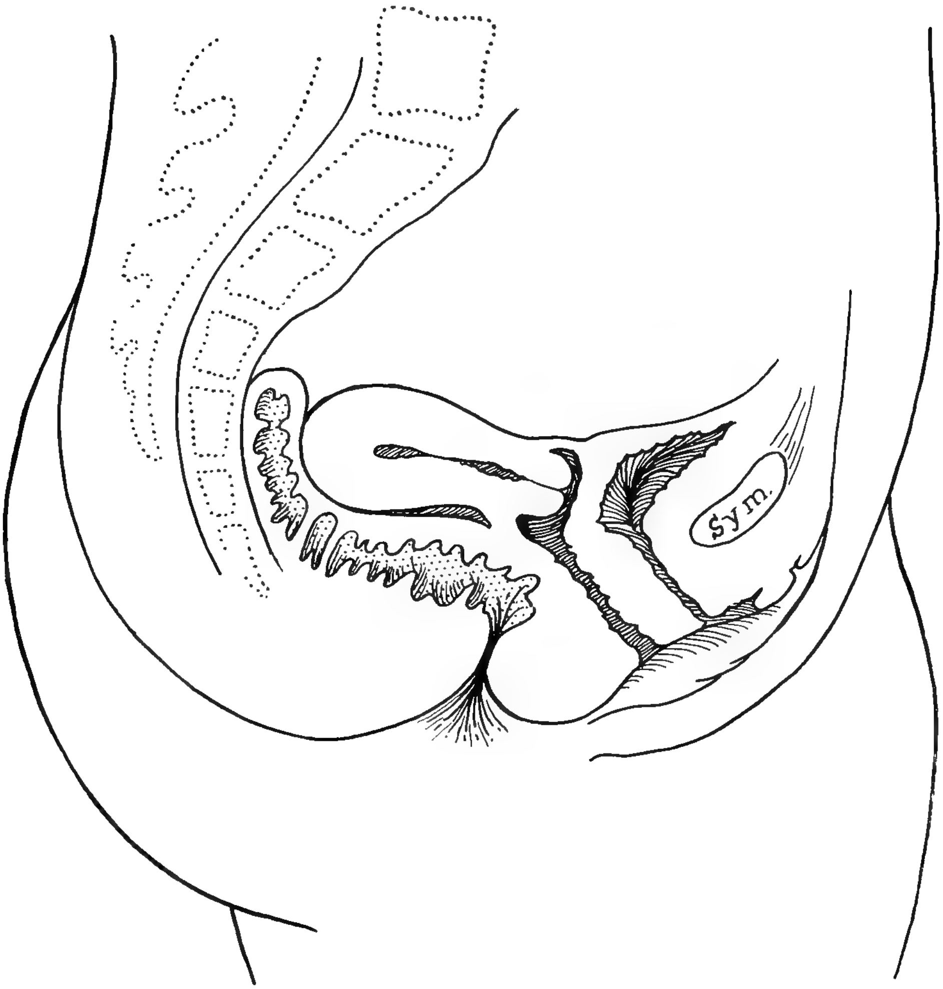

Fig. 283. Retroversion of the uterus. The whole uterus is turned on its axis. The most frequent form of retrodisplacement.

the uterus in a retroposition. In the examination of prepubertal children, one may feel the uterus retroverted not infrequently. Certainly the examination of the adolescent girl shows retroversion rather commonly, though it is increasingly frequent in adult life. In later life, some cases with retroversion undoubtedly are related to childbirth. The uterus is quite heavy in the puerpereum, from its thick walls, hypertrophied muscles, and increased blood volume, and the supporting ligaments may allow the heavy uterus to sink into the cul-de-sac. Often one sees retroversion in early pregnancy, although the young woman had never had retroversion when not pregnant. Evidently the enlarging uterus sinks by gravity into the cul-de-sac in the first six or eight weeks of pregnancy in many instances.

Six weeks after delivery, if the obstetrician finds retrodisplacement of the uterus, he will advise the knee-chest position, or may bring the uterus forward and insert a Smith or Hodge pessary. After use of the pessary for two or three months, complete involution may follow and the uterus may remain in the anterior position. While in the posterior position, the uterus tends to involute less rapidly and remains enlarged to some degree. Later, chronic symptoms related to the sub-

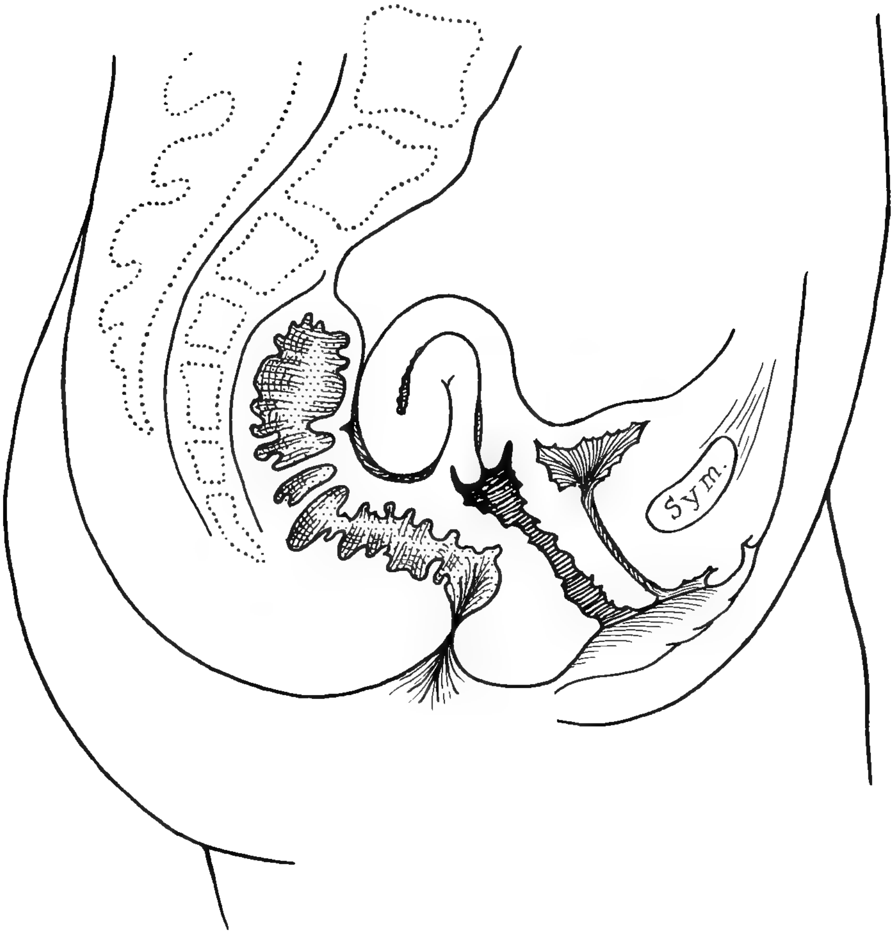

Fig. 284. Retroflexion of the uterus. Marked posterior angulation, in contrast to acute anteflexion. Not as frequent, but it does occur.

involuted, retroverted, heavy, low uterus may develop. From time-to-time the question rises as to whether retroversion may follow a strain or accident. While perhaps this is possible, it has never been documented accurately, and it seems more likely that retrodisplacement that might follow a strain is extremely rare.

Retrodisplacements most often cause no symptoms. On rare occasion, very low discomfort in the depth of the pelvis, a pressure feeling, a bearing down or heaviness, with perhaps some heavy discomfort very low in the sacral region may be caused by retrodisplacement of the uterus. Lumbosacral pain, acute and severe, or chronic and less incapacitating, sacroiliac pain and tenderness, and thoracic back pain, can never be caused by retrodisplacement of the uterus. Constipation probably is never really caused by the retroverted uterus, though perhaps there are exceptions. Marked pelvic pain is not to be expected from retrodisplacement. Dysmenorrhea usually does not accompany the retrodisplacement of itself. Sterility rarely is distinctly related to the retroverted uterus, though in some instances there must be some connection, because the raising of the uterus and inserting a pessary may be followed by pregnancy, perhaps relieving some kinking of the fallopian tubes caused by position and pressure.

On the other hand, dyspareunia may be an important symptom caused by retrodisplacement. In fact, it may be the most important to precipitate any operative surgery. While the majority of people with retrodisplacements do not complain of dyspareunia, and the undersurface of the uterus may be relatively insensitive to the examining fingers, in some individuals this tenderness is extreme, both on pelvic examination and with sexual relations, to such an extent that the normal relations of the husband and wife are completely destroyed.

Retrodisplacement of the uterus is an exceedingly commonly occurring situation in women, and in the vast majority there are no symptoms, the patient's fertility is not impaired, and her normal activity is not restrained. On the other hand, a definite small percentage of cases may have specific complaints related to retrodisplacement. Some may say that this is actually the passive congestion syndrome, or pelvic congestion secondary to the retroversion, that is causing the symptoms. If so, that is immaterial, because the actual retroversion is the real basic cause. Some years ago, enlarged pelvic veins, so-called varicose veins of the broad ligament, were thought to be a cause of many and severe pelvic complaints in women. But, when retrodisplacement is present, that is one of the main causes of the enlarged veins, and correction of the displacement may relieve this congestion, so that to speak of varicose veins of the broad ligament, particularly when retrodisplacement, prolapse, and tumors are present, one refers to a secondary finding. When symptoms possibly related to retrodisplacement are present, and these include pelvic pain and discomfort, pressure, bearing down, and dyspareunia especially, always an attempt is made to elevate the uterus and insert a Smith or Hodge pessary. If improved, the patient may wear this pessary indefinitely, but it should be removed, carefully cleaned, and be reinserted at intervals of six to eight weeks. On the other hand, after a period of time the patient may desire not to wear the pessary, which may not support the uterus properly, may cause discomfort and may cause vaginal irritation, and one may choose to perform suspension of the uterus.

While this clinical test with a pessary has become a well established procedure in gyne-

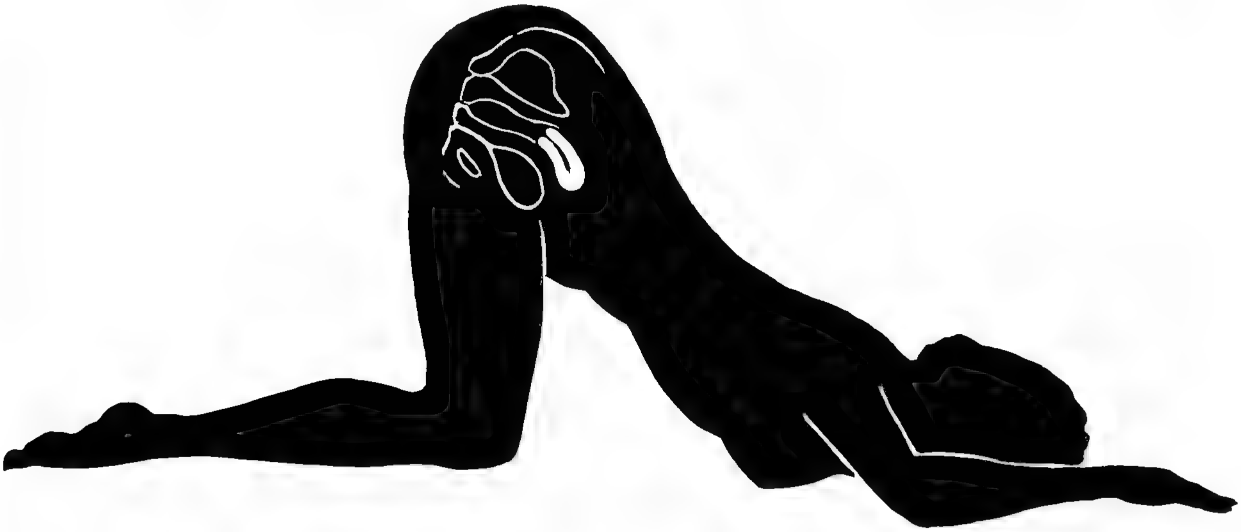

Fig. 285. The knee-chest position. A practical exercise for relieving "congestion" in the pelvis. The uterus is displaced at least temporarily, which aids the circulation. The thighs must be at right angles to the couch, wide enough apart to maintain a stable position. The chest is flat, not supported by elbows or head. The back is purposely made sway-back. Probably this exercise would help the pelvic circulation in the male.

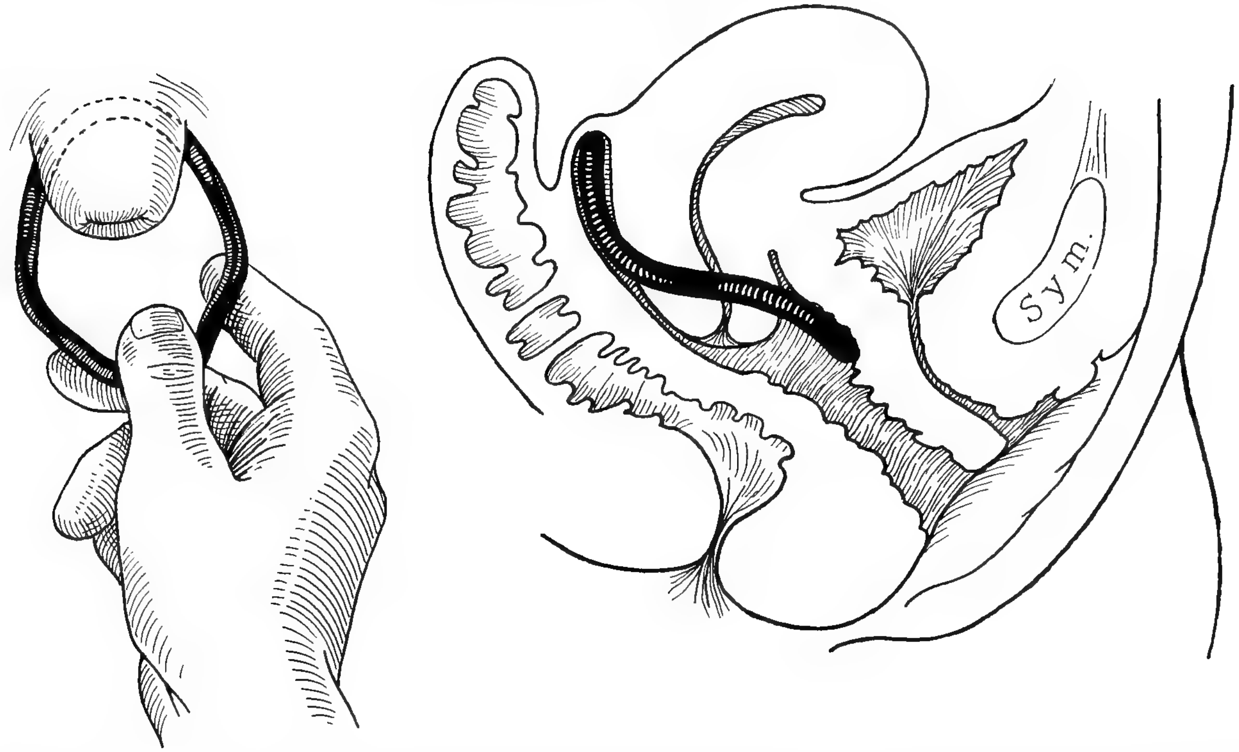

Fig. 286. Use of the Smith pessary for retrodisplacement. The uterus is brought forward, the broad part of the pessary fits behind the cervix, and the more narrow part behind the symphysis. The pressure must not be too great or too little. Ulceration from pressure must be watched for carefully.

cology, in certain instances where the pelvic pain is very definite, and particularly where there is dyspareunia, proper suspension of the uterus would have gained much time for the patient.

In the past ten years or more, suspension of the uterus has become passe in many institutions, and is frowned upon in most, because this operation has been one of the most abused in all surgery. Entirely too many suspensions have been performed for backache (rarely caused by retrodisplacement), for sterility, for constipation, or just because the uterus is not in anterior position. Obviously, to operate on patients to suspend the uterus to cure headaches, or nervousness, is ridiculous. On the other hand, the reaction has swung too far if one feels that suspension of the uterus is not indicated under any circumstances. Suspension of the uterus is especially indicated when endometriosis is present, if operation is necessary, and this has been elaborated upon in some detail in the chapter on endometriosis.

The different methods of suspension of the uterus make up an interesting history in themselves. Before the turn of the century, Howard A. Kelly advised that suspension of the uterus should be performed very frequently. He devised ventral fixation, in which the fundus of the uterus was sutured into the anterior sheath of the rectus muscle, leaving a small opening in the peritoneum to produce adhesions and scarification. Months or years after this type of suspension, commonly an elongated band of tissue extends from the abdominal wall through the peritoneum down to the fundus of the uterus, and this may maintain a fair suspension, but it may not, because the elongation may be such that prolapse of the uterus continues. One of the disadvantages of this form of suspension is the space below the uterus, between it and the bladder, which may allow loops of intestine

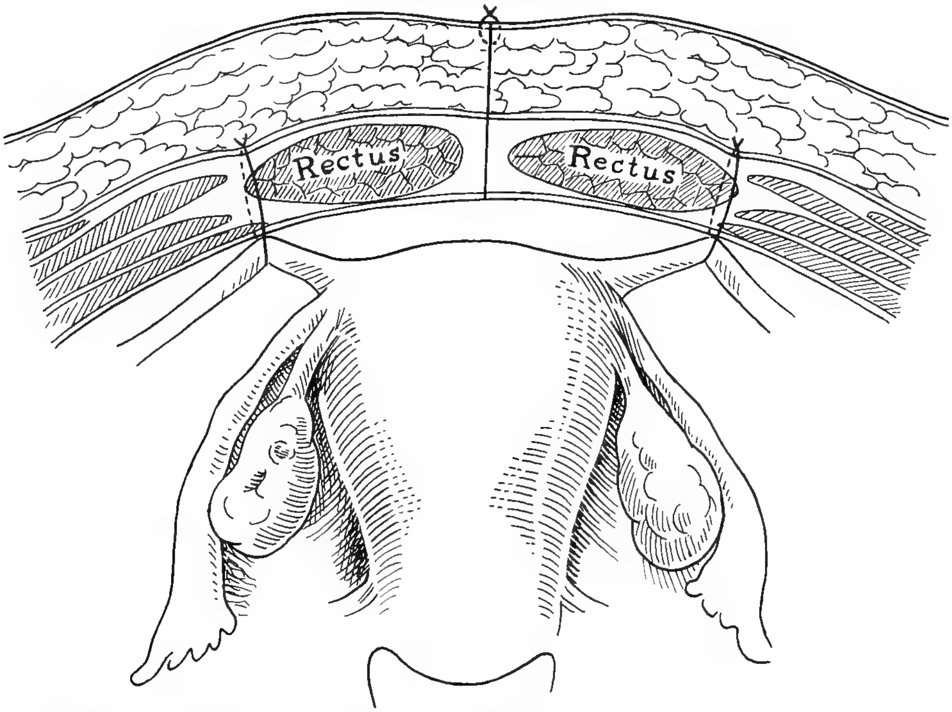

Fig. 287. The Olshausen suspension. Round ligaments are sutured to the abdominal wall by a non-absorable suture extending above the anterior sheath. Note the three cavities or partitions formed, to each side of the round ligament suture and in the center. Loops of bowel may be obstructed by these internal herniae. This method is obsolete.

to be trapped and produce intestinal obstruction. Another type of operation was the Olshausen operation, which drew the round ligaments in their mid portions directly up to the parietal peritoneum by a single suture on each side which extended through the sheath of the rectus. This method produced three small openings in the lower abdomen, the one over the uterus and two lateral to the round ligament sutures. Again, the possibility existed of a loop of intestine being caught in these openings of the surgically produced internal hernias. In the Alexander operation, the abdominal cavity was not opened, but the round ligaments were drawn out through the internal inguinal rings and reattached through lateral incisions in each inguinal region. This was a blind type of suspension, and it was difficult to determine precisely the degree of suspension with this method, as the abdomen was not opened for vision. The Baldy-Webster suspension has been a popular one, in which the round ligaments are drawn through a small opening in the broad ligament and sutured together behind the corpus of the uterus to afford a type of sling, which may hold the uterus in the anterior position. In many instances, this proves a most satisfactory sling, but it does increase tension on the weakest part of the round ligament, as it frays out in its insertion in the loose fascias of the inguinal canal. The fallopian tubes may be distorted by this ligament being drawn beneath them, and small openings in the broad ligament must be most carefully closed to prevent the occurrence of internal hernia. The Emge suspension draws the round ligaments together in front of the uterus, suturing them in this position and attaching them into the corpus. This is not a very anatomical-appearing operation. The last type of suspension to be mentioned is the Simpson modification of the

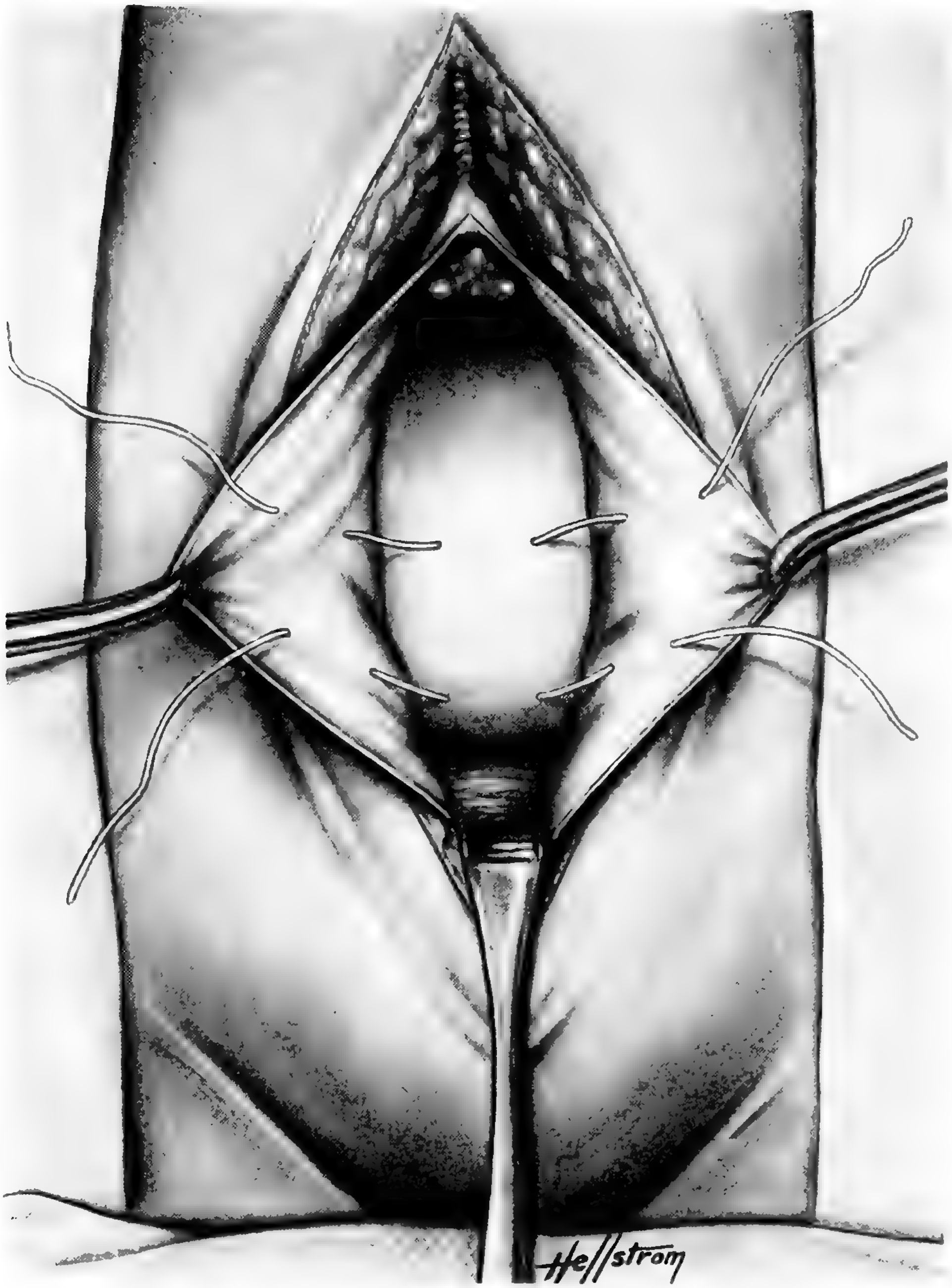

Fig. 288. Ventral fixation of the uterus, suturing the fundus through the peritoneum into the sheath of the rectus muscle. Very frequently performed years ago, passe today. Not infrequently older patients are seen who have had this operation.

Gilliam operation. Actually, the original Gilliam operation drew the round ligament through the inguinal ring and sutured it superficial to the heavy rectus fascia. The Simpson modification draws the ligament through the internal inguinal ring, and sutures it to the undersurface of the fascia of the rectus muscle. As a rule, this is a satisfactory form of suspension of the uterus. Occasionally, when the fundus of the uterus extends above the insertion of the round ligament, and particularly when it is congested and enlarged from its long retroversion, it may seem to droop over backward after this type of suspension and not be held completely in anterior position. In some of these cases, the suspension is not quite satisfactory. As a rule, with suspension of the uterus, the uterosacral ligaments are plicated and reattached to the back of the cervix to shorten them and draw the cervix up into the abdomen, because degrees of descensus are common with retrodisplacement. Small portions of the posterior broad ligaments often are brought across and sutured together behind the lower part of the corpus with fine sutures, which adds to making a small hammock to lift the uterus forward.

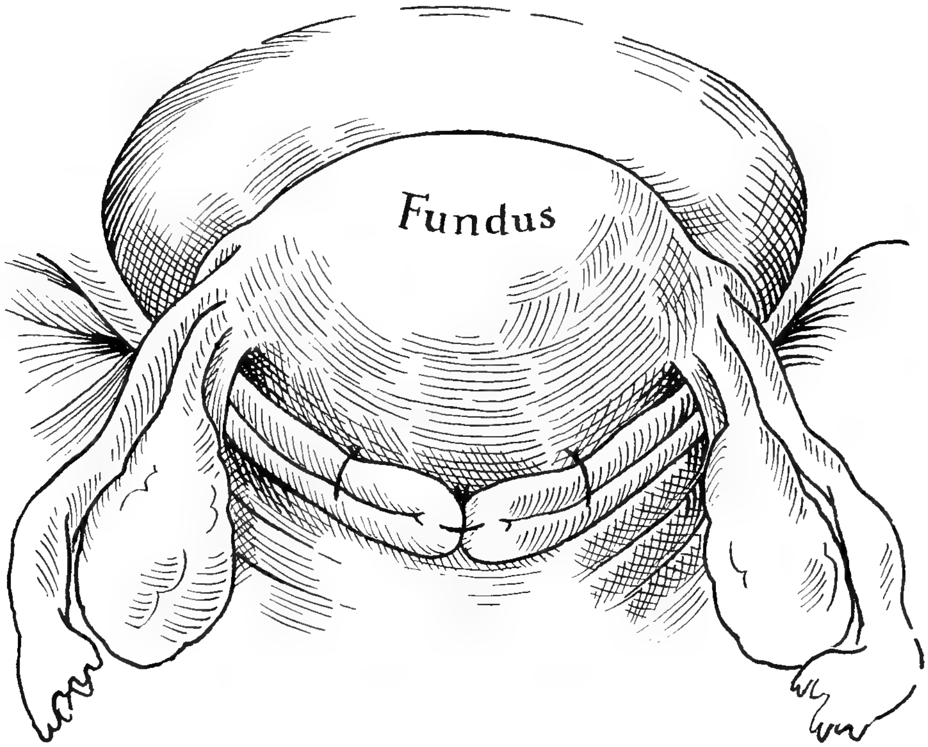

Fig. 289. Baldy-Webster suspension. The round ligaments drawn through an opening made in broad ligaments and attached together behind the corpus. The pull continues on the weaker insertion of the round ligaments which fray out in the inguinal canals.

VESICO-VAGINAL, VESICO-CERVICO-VAGINAL, AND URETERO-VAGINAL FISTULAS

In the progressively distant past, or near distant past, the majority of urinary fistulas followed complications of delivery, and were related to lacerations from the cervix extending into the bladder, to necrosis of the bladder from prolonged labor with incarceration of a fetal part, and to difficult extraction, whether by manual means, or more frequently by the use of forceps. Now, with better obstetric teachings, with the more careful observation of the patient during labor, with the more prompt use of Caesarian section when necessary, with the methods of stimulating labor when properly indicated, and with the now almost absent use of high forceps and infrequent use of mid-forceps, and finally with a more careful understanding by the physician of the application of forceps for extraction of the head, these injuries due to obstetric delivery are very infrequent. That they will

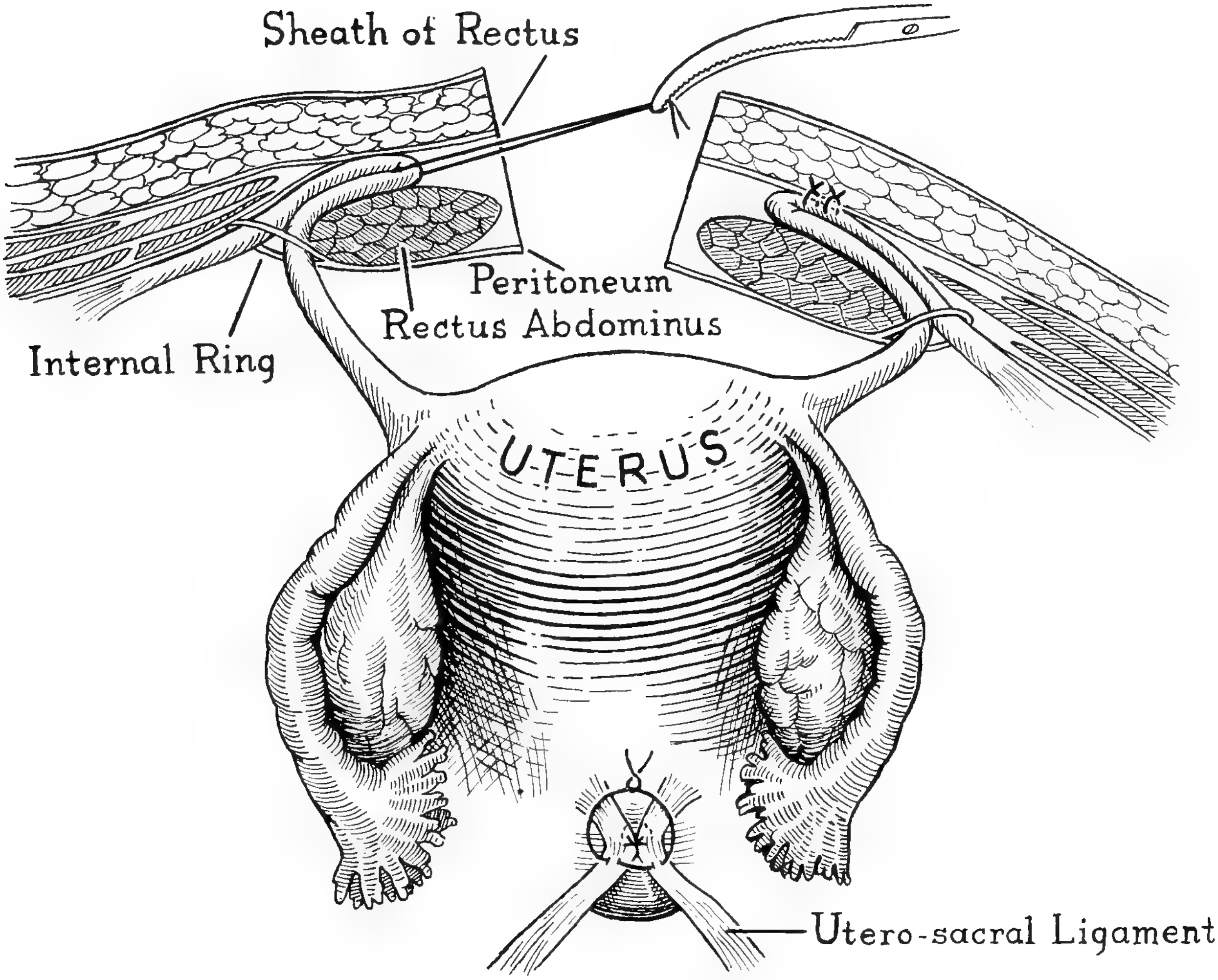

Fig. 290. Simpson modification of the Gilliam operation. A guide suture, placed 1½ inches from the cornu, is drawn through the internal inguinal ring. The round ligament is sutured to the undersurface of the anterior sheath of the rectus muscle with silk or cotton. The uterosacral ligaments are plicated and attached to the back of the cervix for shortening. Though suspension of the uterus is rarely performed today, this is the preferred method when the operation is indicated.

continue to occur occasionally is obvious, because of expected complications or misjudgement, which may occur with any person.

The second cause of urinary fistulas is invasive carcinoma, particularly invasive carcinoma of the cervix. This destructive tumor not only eats away the cervix and the lower part of the uterus, but the adjacent vaginal walls including the wall of the bladder, so as to erode into the interior of the bladder and produce large and incurable fistulas. Similarly the growth may invade and destroy the wall of the ureter, and allow the urinary drainage from the ureter into the large cavity that may form from the destruction by the carcinoma of the cervix. Other cancers, whether arising in the uterus, or more particularly in the vagina and bladder, may cause similar urinary fistulas. The occurrence of these fistulas is being reduced as malignant disease is being found in much earlier stages, and perhaps the lesion will even disappear if all carcinoma-in-situs are treated vigorously. Again, some people always will refuse examination, treatment, or follow-up, so that occasionally regardless of progress, this type of fistula will be found.

The third most common cause of urinary fistula in the past has been destruction from the use of radium in the treatment of carcinoma, particularly carcinoma of the cervix, but also carcinoma of the vagina and bladder. The necrotizing effects of radium may continue for some years after its application, but rapidly occurring ulcerative destruction may occur within a few weeks of its application. When such destruction occurs, due to radium, usually there has been a "hot spot," the radium has been too closely applied to the bladder, without proper shielding or the use of packing to hold the bladder wall one or two cm. from the radium applicator. In spite of the greatest precautions, the applicator may slip from its original position; in fact, this commonly occurs because there is no direct fastening of the applicator into its position, and after even minor muscle activity in bed, and bladder and bowel action, the applicator must vary considerably in its location. The other factor in fistulas that occur after irradiation is the increasingly large dosage of radium and roentgen therapy being used in recent years. Because cancer of the cervix may be cured in a generous percentage of cases in its early stage by a relatively small dose of radium, as 3000 mgm. hours applied to the cervix, it has been thought that failures, recurrences and extensive lesions may be cured if larger and larger amounts of irradiation are used; as a local application of radium or cobalt, as the interstitial application of radium by needles containing radium or cobalt, and external roentgen therapy, including the million-volt, two million-volt x-ray machines, high dosage radio-active cobalt and betatron units. Unfortunately, it is not true that if a small dose of radium will cure some cancers of the cervix like magic, that an extremely large dose will cure the remainder. Undoubtedly the cure rate is increased by the larger doses, but not to the degree that one might expect. The late effects of the present day extraordinary amount of irradiation therapy (with 6000-6500 r. tumor dose to the lymph node areas, and tremendously larger doses to the cervix and its surrounding tissues) will be seen in increasing numbers of patients in the future; not only will there be seen fistulas of the bladder and ureter, but many other destructive effects following the intense irradiation. This includes severe fibrosis and telangiectasia of the abdominal wall, the tremendous thickening of the wall of the bowel which is in the line of the beam of the irradiation therapy, unknown changes in the nerves, and decalcification of the bones of the pelvis and femurs. Absorption of bone and pathological fractures are being seen with increasing frequency. Because irradiation therapy is one of our most effective methods, and often a life-saving procedure, in the treatment of cancer of the cervix, and other forms of genital cancer, such therapy necessarily will continue to be used when the lesion is well-formed and not in the non-invasive stage, or until a better method of therapy is found. Surgical treatment alone has its adherents in these invasive tumors, but this therapy, too, has its disappointments and complete failures. There is no satisfactory treatment for advanced cancer.

The fourth most frequent cause of urinary fistulas in the past has been surgical operations. At the present time, this cause of fistulas is coming to the forefront, and they will be seen more frequently because of increasing numbers of pelvic operations being performed, because of the almost routine use of total hysterectomy in contrast to subtotal hysterectomy in the past, because of the extensive amount of vaginal repair work, and because of the radical surgical approach to carcinoma of the cervix that is being used with increased frequency throughout the country. They are related both to accidental incision of the bladder in various operative procedures. which is not recognized at the time of surgery, and is not sutured closed, and to the fact that the bladder is not completely mobilized from the region of the cervix, and is accidentally and unknowingly cut into in excising the cervix, and the fact that the sutures in the vaginal cuff may be placed through the bladder wall and mucosa unknowingly and cause a delayed fistula some ten or twelve days following the total hysterectomy.

The uretero-vaginal fistulas that may follow the conservative total hysterectomy also are related to unknowingly cutting the ureter or clamping it so as to destroy its blood supply and irrevocably injure its wall, and to placing sutures about it as to partly constrict the ureter. These complications occur when the ureter is placed abnormally close to the uterus, when there are large inflammatory masses or endometrial cysts, when there are large uterine tumors which may be intraligamentary, or when there are other rare and unusual situations in the pelvis encountered at pelvic surgery. The greatest care is necessary to avoid the ureters even in the simplest pelvic operations. Many have advised, especially the urologists who see these complications, the use of ureteral catheters routinely before any pelvic surgery is performed. At times this may prove a great convenience for the surgeon and safety for the patient, but as a rule most gynecologic surgeons prefer to trust their knowledge of anatomy and to avoid the traumatic effects of the intra-ureteral catheter, which trauma may possibly be a factor in the formation of fistulas.

The number of fistulas which follow the radical surgical procedures, particularly the Wertheim radical hysterectomy and pelvic lymph node dissection, which is being used with increasing frequency in the treatment of carcinoma of the cervix, both with and without preoperative irradiation therapy, is a main source of urinary tract fistulas being seen at the present time. From eight to sixteen per cent of the cases having radical hysterectomy and lymph node dissections have been followed by vesico-vaginal or uretero-vaginal fistulas. This percentage is so high because of the very radical nature of the stripping of the pelvis and ureters and mobilization of the bladder, in which the blood supply to the ureter and bladder has been damaged irrevocably, because of unrecognized tears or incisions into the ureter or bladder which are not resutured, and particularly because of devitalization of the adjacent bladder and ureter from pre-operative radium therapy. With increasing understanding of the necessity of the protection of the blood supply to the ureter by leaving it attached to the posterior layer of the broad ligament peritoneum as far as possible down toward the cervix, and by not stripping it too cleanly of its adjacent connective fatty tissues, and by avoiding preoperative radium in any intensive degree, the frequency of fistulas following radical hysterectomy should diminish, and in fact they should approach one or two per cent of cases.

The fistula that follows cystocele repair, or cystourethrocele repair, are not as frequent as those seen after the conservative abdominal total hysterectomy, but they do occur. Incisions are made into the bladder unknowingly occasionally; when properly sutured together in layers, generally the healing is normal. The urethrovaginal fistulas particularly may follow repairative plastic vaginal surgery, probably due to the dissection extending into the urethral lumen unknowingly. Similarly, vesico-vaginal fistulas follow vaginal hysterectomy, that operation which is becoming so very popular at the present time. Mobilization of the bladder from the uterus in the early stages of the operation may produce an entrance into the interior of the bladder, and unless this is noted immediately and closed in layers, a fistula is to be expected.

The most frequent urinary fistula of this day seems to be the vesico-vaginal fistula which follows conservative abdominal total hysterectomy. It is caused, as a rule, by incomplete mobilization of the bladder from the cervix and adjacent vagina before removing the cervix, and by the insertion of closing sutures through the bladder wall.

The diagnosis of urinary fistulas is not too difficult as a rule. The patient knows her difficulty. The insertion of a dye, as methylene blue or indigocarmine, or sterile milk, in the bladder quickly determines the bladder fistula. Cystoscopy, ureteral catheterizations, pyeloureterograms, and intravenous indigocarmine clarify the position of ureteral fistulas. The ectopic ureteral opening in the vagina is a rare cause of urinary leakage.

TREATMENT OF VESICO-VAGINAL AND URETERO-VAGINAL FISTULAS

Any discussion of the repair of vesico-vaginal fistulas would be incomplete without some tribute to the great American gynecologist, Marion Sims. While practicing medicine in a small town in Alabama, in the middle of the nineteenth century, Marion Sims encountered numerous vesico-vaginal fistulas following obstetric complications, particularly occurring in colored women, who had had difficult, prolonged labors, and frequent use of forceps because of their small pelves. He began his operative procedures, using different methods to attempt to repair these fistulas. Efforts at resuturing these holes in the bladder were largely futile, because various forms of suture used in these closures, mainly the non-absorbable silk and linen sutures, became involved in local infection, sloughed out, and caused the fistula to reform as before. Finally, Sims used through-and-through sutures of silver wire, which were left in place for a long period, which obtained for his patients better results than any before. The silver wire suture does not cause inflammation about it, or only to a minor degree, being relatively inert as compared with other non-absorbable sutures. As a rule, after weeks or months, the silver wire sutures were divided and removed.

Following Marion Sims' early reports in the literature, which included a description of the Sims left lateral position (the patient lying on the left side, the left leg fairly straight and the right leg flexed, which allows the pelvic outlet to be displaced up, out and somewhat forward) and the Sim's speculum (used to elevate the perineum and vaginal wall, allowing distention of the vagina with air and increase in vision and operative space), he was invited to New York where he demonstrated his operative techniques. Subsequently, he went to Paris and operated on Empress Eugenie, apparently curing her vesico-vaginal fistula. He returned to New York and was the first Chief of Staff of the Woman's Hospital, beginning the illustrious history of the hospital. Sims was an extraordinary man, with great ability and numerous interests in gynecology, making many contributions. He advocated the study of spermatazoa in cervical mucus, in cases with sterility, which was known as the Sims test, more recently called the Huehner test, and now more popularly known as the Sims-Huehner test. Sims was a controversial figure in American medicine, being criticized for his study of spermatazoa in the cervical mucus, and also because of his varied arguments within the profession over other matters. Today he remains one of the great figures in Gynecology.

The modern treatment of vesico-vaginal fistula is based on the following points: the inflammation and induration in the edges of the fistula must subside by allowing a proper amount of time to pass after the formation of the fistula, particularly after surgical or obstetrical causes (and for this reason those following irradiation therapy or malignancy rarely can be closed), proper and complete mobilization of the layers of the bladder and vagina separately, excision of the edges back to healthy, normal tissue, careful and meticulous closure in layers with absorbable suture material (fine chromic catgut), complete drainage with the large urethral catheter or suprapublic catheter, or vaginal cystotomy, and careful antibiotic therapy.

In those fistulas which have formed after operations and obstetric delivery, ordinarily, in the past, one has waited six months before attempting to close these fistulas. Now, with the antibiotics, and more particularly with the use of cortisone, the inflammation and induration in the bladder and vaginal walls about the fistula may be rapidly dissipated, and closure of the fistula may be attempted at much earlier times, possibly six weeks to three months after their formation. A few surgeons have closed these fistulas within ten days or two weeks, following their occurrence. Many such procedures have been doomed to failure, but possibly cortisone and careful mobilization, more widely performed by abdominal approach when the fistula follows abdominal total hysterectomy, will allow success in some operations performed soon after occurrence of the fistula. As a rule, two or three months should intervene, and all of the aids of present antibiotics and hormone therapy should be used to remove the barrier or obstruction to healing of the repaired fistula. In the majority of the cases, these cases are approached through the vagina, possibly using the knee-chest position, Sims left lateral position, or the lithotomy position (patient on her back with legs elevated). In the latter approach, the Schuchardt incision, a lateral episiotomy opening the vagina to its apex, dividing the levator muscles and reflecting the rectum to the opposite side, may be most advantageous for exposure of the high fistula. Some of the fistulas at the very apex of the vagina, particularly those following abdominal total hysterectomy, have been closed by the Latzko method, which closes the upper portion of the vagina in layers and thus shortens the vagina and forms a small diverticulum at the point of the fistula. While this may be successful, it has theoretical and practical disadvantages.

The abdominal approach to the repair of these fistulas is not to be underestimated. If the abdomen and pelvis is not too deep to be able to expose and mobilize the layers of vagina and bladder, repair of the apical fistulas may be performed with greater success in some cases with this approach. Gentleness and care in the mobilization of the tissues and the introduction of the sutures without undue tension are necessary for the success of these operations. Recurrence after surgical repair is most disappointing.

When extremely large defects have occurred in the base of the bladder, such that they cannot possibly be closed by mobilization of tissues (surprisingly this mobilization may be accomplished in some instances by extraordinary lateral dissection), the vagina may be closed entirely at its orifice, so that the vagina is made a part of the bladder. To produce a water-tight healing by this closure may be difficult and may require more than one attempt for complete closure. This procedure may be successful, provided the internal sphincter at the vesical neck is intact and able to maintain urinary control. Menstruation necessarily has ceased.

In other instances, by means of extensive mobilization, the fundus of the bladder may be drawn forward under the trigone and tucked into the defect (Kelly). The transplantation of portions of the vulvar skin and the superficial muscles about the vagina, and even the pubococcygeus muscle, may be used to fill extensive defects. Extraordinary plastic effects are possible, with imagination and daring. In some instances, of course, it appears impossible to close these defects, and when the sphincter of the bladder has been destroyed, any attempt at closure is unsatisfactory, because of the continuous drainage of urine from an incompetent urethra and bladder neck. In such instances, one prefers to transplant the ureters, either to the sigmoid, or to an isolated segment of the terminal ileum, which collects the urine and directs it out an opening in the right lower quadrant of the abdomen into a bag of plastic material, sealed to the abdominal wall. This Bricker conduit procedure is one of the better approaches to urinary diversion of today, because of lessened ascending pyelonephritis.

Skin ureterostomy may be used occasionally, but is not as satisfactory, because of difficulties in collecting the urine from the small openings, and because of the repeated strictures that develop in the ends of these ureters.

The repair of ureterovaginal fistulas may produce quite a problem. The cause of the fistula usually signals the future treatment. If it develops immediately after abdominal total hysterectomy, one would assume that the ureter has been divided completely at the time of operation. If it develops in the first two or three weeks following surgery, one would assume that the ureter was crushed or that its blood supply was interrupted, causing some sloughing of the wall, perhaps only on one side. Some of these instances may be followed by spontaneous healing, without destruction of the kidney. On the other hand, more of them probably eventually need surgical intervention, especially if one attempts to save the involved kidney. Probably many of those that appear to heal spontaneously, and not too many of them do, heal by complete occlusion of the ureter, with a subsequent dead or non-functioning kidney.

If one ureter has been ligated at the time of operation, and if this can be determined in the first few days, possibly from the development of flank pain and the use of the intravenous pyelogram showing non-drainage of urine from one side, the better procedure probably is to reoperate immediately and remove the ligature. The diagnosis is difficult, though more obvious if both ureters are ligated, because of anuria. In each instance the diagnosis is confirmed by the inability to catheterize the ureters above a certain level. More likely excision of the involved portion and re-anastamosis of the ureter with fine catgut sutures over the ureteral catheter would be necessary. If the patient is in serious condition, and if one ureter is draining urine normally, often it is better to allow the other kidney to become functionless and atrophy. On the other hand, one prefers to save a kidney when possible, because subsequent pathology might develop in the remaining kidney. Much more interest in saving the involved kidney has developed in recent years.

For the ureteral fistula, one may insert the ureteral catheter into the kidney, if possible. The catheter drainage may be followed by healing of the fistula after two or three weeks, and this would certainly be a happy outcome. More often the catheter cannot be inserted up to the kidney, due to ligation or sloughing, or displacement of the ends of the ureter, and operative procedure is necessary. Again the antibiotics are used to remove all inflammation possible, and cortisone may be used to absorb induration in the edges. Surgical repair by careful mobilization of the ends of the ureter, excision back to normal tissue, and end-to-end anastamosis are indicated. If anastamosis cannot be made, one may attempt to suture the ureter into the apex of the bladder. Even a portion of the bladder may be cut away and fashioned into a tube, making up one or two inches to reach a shortened ureter. In some instances no possible connection can seem to be made, and the ureter is either ligated, if no infection is present, allowing the kidney to become atrophic, or one may make a flank incision and remove the kidney to prevent further complication. Always, one must be certain of the status of the other kidney when any urinary tract operative procedure is attempted.

RECTOVAGINAL FISTULA

Rectovaginal fistulas have occurred in the past particularly following difficult deliveries and the use of forceps which have pinched, torn, or lacerated a portion of the vaginal wall and rectum, and following invasive carcinoma of the cervix, vagina and rectum, and the destructive effects of irradiation in the treatment of these carcinomas. Since the complications of delivery have been greatly reduced with modern and better obstetrics, in which much greater care is exercised in the use of forceps, and in which Caesarian section is resorted to more frequently when necessary for prolonged and difficult labor, and since carcinoma of the cervix is being discovered at much earlier intervals than some years ago, particularly since the development of cervical cytology and discovery of carcinoma-in-situ, the vigorous treatment of which may eradicate carcinoma of the cervix, and since the techniques of irradiation therapy, while becoming more intensive in many areas, are practised with much greater care and protection of the adjoining organs, fistulas from these origins seem to be diminished greatly in their occurrence at the present time, and probably will be further diminished

It would seem that the more frequent causes of rectovaginal fistula today are those following operations. Perhaps the most frequent is a complication of perineorrhaphy. In the dissection of the rectum from the vagina in the perineal repair, small incisions or tears may be made through the rectal mucosa unknowingly, and may be followed by rectovaginal fistula. While fortunately this is not frequent, it does occur even in the experience of the best. If only one can determine that such an incision has been made and proper resuture is performed immediately, probably the fistula will be averted, as with the bladder fistulas. The recognition and immediate restoration of the integrity of the wall of these organs is the key to the best treatment. Also these fistulas occur occasionally following excision of the chronic Bartholin's gland abscess or the Bartholin's gland cyst. This diseased tissue may extend closely to the rectal wall. In the dissection and excision of the gland, the rectum readily may be tented up, pulled into an abnormal position, and cut across accidently, entering the lumen of the rectum. Perhaps the more frequent use of the marsupialization procedures for the Bartholin gland cyst and abscess will diminish the occurrence of these fistulas, although this window-making operation may lose its popularity, and a return to total excision of the gland may be a future development.

Less frequently fistulas may follow rectal surgery, as after the excision of high internal hemorrhoids, various ramifying anal fistulas that may extend anteriorly into the rectovaginal septum, and the drainage of a rectovaginal wall abscess, which had arisen from a rectal sinus tract. But more frequently the fistulas are associated with the gynecological surgical procedures, not only after perineorrhaphy, episiotomy, and excision of the Bartholin glands, but also after abdominal total hysterectomy. This may occur after various pathological conditions associated with the uterus and adnexa, including severe inflammatory disease, and particularly pelvic endometriosis, when it involves the cul-de-sac and rectovaginal septum. While, as a rule, if the dissection is made by cutting very close to the cervix, one soon enters a line of cleavage and separates the rectum from the cervix and vagina with little difficulty, yet the rectum may be entered at this point. Most authors have stated that one of the indications for subtotal hysterectomy is extensive endometriosis, but this is not true very often.

In the surgical treatment of rectovaginal fistula, nearly always one must wait a considerable period of time after the fistula has developed before attempting to close it surgically, and this is particularly true of those developing after delivery and after operations. After four to six days following perineorrhaphy, or following abdominal total hysterectomy, there may appear suddenly the distressing extrusion of gas and fecal material into the vagina. In some instances only the gas seems to pass through, and little or no fecal material. But, as a rule, after the fistula has formed in the early stage, it becomes two or three centimeters in diameter and seems a drastic and tragic situation to all concerned. No possible closure of the fistula can be made at that time. If one calmly allows this to continue in its way, retraction and narrowing of the fistula will follow, with gradual disappearance of the inflammatory reaction about its edges. A rectovaginal fistula two centimeters in diameter may become so small that one can hardly pass a probe through it; in fact, after one or two years, the patient may have no further complaint, and may not wish it closed. Perhaps more of them will be bothered by the passage of gas through the vagina, and the seepage of fecal material. At any rate one does allow a thorough period of time for regression. Perhaps this may be shortened by antibiotics, and at certain stages, with the short term use of cortisone.

The surgical technique of the repair of rectovaginal fistulas varies according to the position along the vagina. If the fistula is quite low it may be dissected out, and repair performed in layers, first of the mucosa, then the rectal wall and its fascia, the levator muscles, and finally the vaginal mucosa. This must be followed by cutting the sphincter of the rectum, preferably at six o'clock. Some have advised that the sphincter be cut at four and eight o'clock (Miller), but since the fibers of the muscle decussate posteriorly in the midline, and anteriorly in the midline, it seems better to make the single incision posteriorly, avoiding the other superficial tissues anteriorly. This incision is followed by firm healing with reformation of the sphincter, as a rule.

A second method of repairing these fistulas, especially if it is placed one-third or half way up the vagina, is to convert the fistula into a third degree tear, making a fresh incision through the perineum, sphincter, vagina and rectum up to the fistulous opening. The thickened tissue around the opening is excised, the rectal mucosa closed with interrupted silk with knots on the mucosal side for sloughing, the rectal wall closed with catgut, levator muscles approximated in the midline, vaginal mucosa closed, sphincter approximated and reinforced with silk, and finally the perineum closed. Again the sphincter is divided posteriorly. It is so very important to relieve all of the pressure of gas in the rectum by allowing it to seep out with ease. Any continued pressure, most likely from gas, but possibly from fecal material, may cause a break-down of the fistula repair.

A third method of repairing fistulas that are relatively low near the sphincter is to mobilize the mucosa of the rectum from the rectal side, and attach it to the mucocutaneous junction of the anus, after excising the intervening mucosa. This sliding operation has been followed by excellent results in the hands of the proctologist and the gynecologist (Mengert). Again, the sphincter is divided posteriorly.

The fourth method is the abdominal approach for the fistula at the apex of the vagina, which has followed hysterectomy. These are approached from above in order that thorough and complete mobilization of the rectosigmoid may be obtained, after which the thickened and scarred areas in the rectum or rectosigmoid are excised and the bowel wall closed in layers, reinforcing the bowel wall with extra sutures. The vagina then may be closed or left open, as desired in the usual hysterectomy technique, although the peritoneum is always closed over the opening of the vagina. This latter operative procedure, and all the other fistula operations, are preceded by intestinal preparation, including sulfasuccidine or sulfathalidine and neomycin. Postoperatively these antibiotics are continued in addition to other parenteral antibiotics as indicated.

The fifth approach to closure of these fistulas is the extensive operative procedure, such as suggested by Bastiaanse of Amsterdam. In the large fistulas that follow radium applications for carcinoma of the cervix or extraordinary and extensive fistulas after some obstetric complications, and if no residual carcinoma can be found. Bastiaanse has advised an extensive procedure for closure of these fistulas. Both the vaginal and abdominal approach may be used. First the fistula area is completely mobilized, if necessary with the additional Schuchardt incision and the combined abdominal approach, the scar tissue is excised, and the fistula is closed, if necessary by drawing the sigmoid wall far down and overlapping the fistula. In others the omentum may be mobilized by dissecting free from its colonic attachment on one side and turned around in order to lengthen it in its middle, and allow it to extend well down into the vagina. Various portions of the vulva and external vaginal muscles, and the levator muscles may be mobilized and placed over extensive fistula areas, for re-inforcement of the sutures. These unusual operative procedures have been used to close the advanced, difficult and seemingly impossible fistulas.

A sixth approach to the large fistulas is the colostomy alone. Of course, the temporary colostomy may be used in many of the closures of these fistulas to put the bowel at rest, and may be used more frequently by some operators than others. As a rule, if proper intestinal preparation and postoperative antibiotics are used, if the closure can be made without undue tension, and if the sphincter is divided with the lower fistulas, colostomy probably is rarely necessary. But with large distressing fistulas, associated with recurrent and active carcinoma, which cannot possibly be cured by any treatment, colostomy may give partial relief, at least from continuous soiling by fecal material from the vagina.

A seventh approach to these fistulas caused by carcinoma, often involving both the bladder and rectum, is the exenteration operation, removing either the pelvic organs and rectum, or pelvic organs and bladder, or bladder, pelvic organs and rectum together. In these last cases the procedure is performed primarily for the carcinoma, and entirely secondarily for the fistula.

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CHAPTER XII

Diseases of the Placenta and Early Pregnancy

The young placenta at six weeks of age has a much smaller number of villi than the adult placenta, but these individual villi are quite larger than those of the adult placenta, about six to ten times the size of the mature ones. The quite young villi contain no central blood vessels, and must rely on their nourishment from absorption of nutrients from the adjoining cells and tissue fluids. The interior of the villus is composed of very loosely arranged fibroblastic or myxomatous tissue, containing large, and very pale staining, cells with minute nuclei.

The surface of the chorionic villus is covered with trophoblast. The trophoblast consists of two types of cells. The inner layer of cells is a single layer of cuboidal epithelium. The outer layer is imperfectly covered with syncytium, which means large giant cells with multiple nuclei, in which the cytoplasm seems to be poured onto the surface of the villus, in places piling up as projecting masses with multiple nuclei. In some areas, the amount of syncytium on the surface is scant, whereas adjacent areas have large portions of cytoplasm containing multiple nuclei.

The trophoblast which belongs to the embryo and fetus, and not to the mother, has potent functions. The inner layer of cells, known as the Langhan's cells, is the origin of the secretion of chorionic gonadotrophin, while the syncytium is the origin of the large amounts of estrogen and progesterone which appear during pregnancy. When the pregnancy is six weeks old, the inner layer of Langhan's cells is quite prominent, later to become atrophic and even seem to disappear at term. When the cells are quite prominent, a very large amount of chorionic gonadotrophin is present in the blood stream and spills over into the urine, so that the highest peak of this hormone occurs with the six weeks old pregnancy. Later the level falls quite rapidly to a relatively small amount after the third month of pregnancy. For this reason, the numerous tests for the detection of pregnancy by determining the presence of chorionic gonadotrophin are most accurate when the pregnancy is of six weeks duration. After three months of pregnancy, not infrequently the pregnancy tests are negative, because the level of chorionic gonadotrophin is so low.

The syncytium also is quite prominent in the placenta six weeks old. At this time, there is secreted considerable amounts of progesterone and estrogen into the blood stream, which are partly metabolized by the liver and excreted as metabolites, and in part are excreted by the kidneys in the original form of the hormone. While the syncytium may not appear quite so prominent as pregnancy progresses, yet the number of villi increases remarkably in number, and the large size of the placenta means that a much larger number of syncytial cells are present. This explains the increasing titers of estrogens and progesterone up to a very short time before labor ensues.

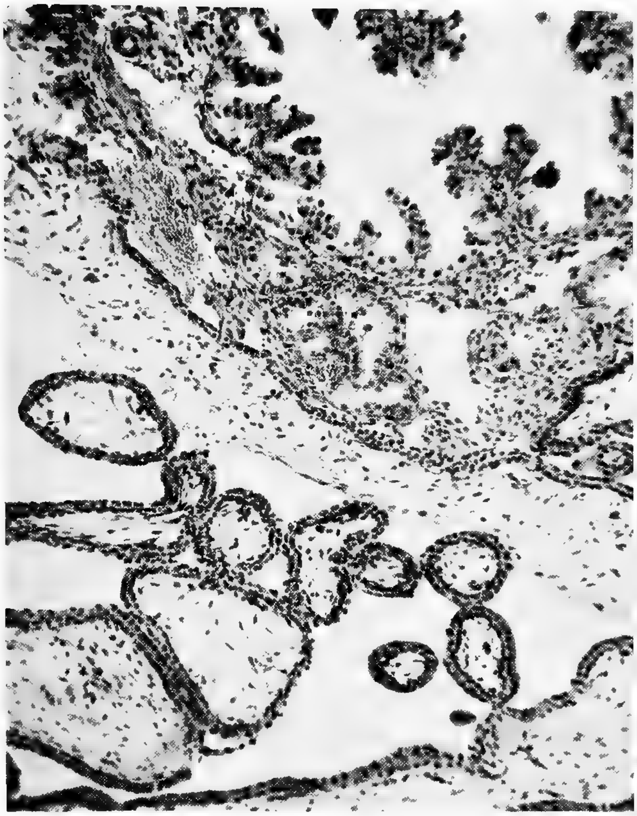


Fig. 291. Young pregnancy with premenstrual endometrium. The villi have no blood vessels, are lined with a double layer of cells, which are quite distinctive, the inner layer of Langhan's cells and outer layer of syncytium. The endometrial glands show a marked saw-tooth appearance, the epithelial cells are irregular, having discharged their glycogen into the lumen.

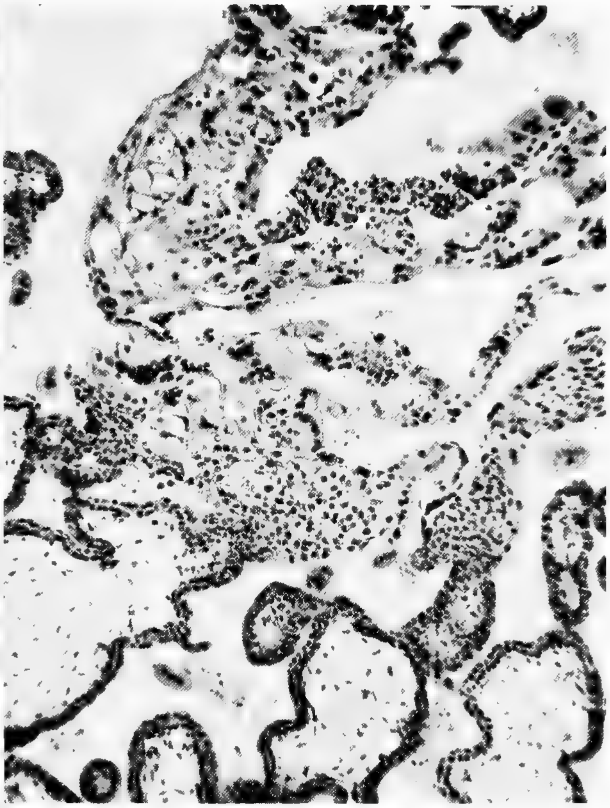


Fig. 292. Young pregnancy with marked proliferation of trophoblasts; normal. The villi show no blood vessels. The proliferation of both Langhan's cells and syncytium is remarkable, may be interpreted as malignancy, but is normal in this instance.

ABORTION

Spontaneous abortion occurs most commonly when the pregnancy is six weeks to three months of age. Practically every married woman has had one or more spontaneous abortions in her married life. In some instances, repeated spontaneous abortions may occur. If abortion occurs four or five times consecutively, the condition is called habitual abortion. The causes of spontaneous abortion are largely unknown, but there are certain factors of interest and importance.

Thirty years ago, Streeter demonstrated that examination of the embryoes from patients with abortions showed the occurrence of congenital abnormalities in a large percentage. This gave rise to the idea that most abortions are inevitable abortions, that nature is wisely sloughing them out, that the concept of a "blighted ovum" is the explanation for the majority of spontaneous abortions. This is a comforting answer, and makes one philosophic regarding abortions.

On the other hand, there are numerous avenues that are suggested for the prevention and cure of threatened abortions. Suggested causes include an abnormal hormonal status, particularly a subnormal amount of progesterone or estrogen. For many years, great interest has existed in the possibility of a diminished progesterone level, and this

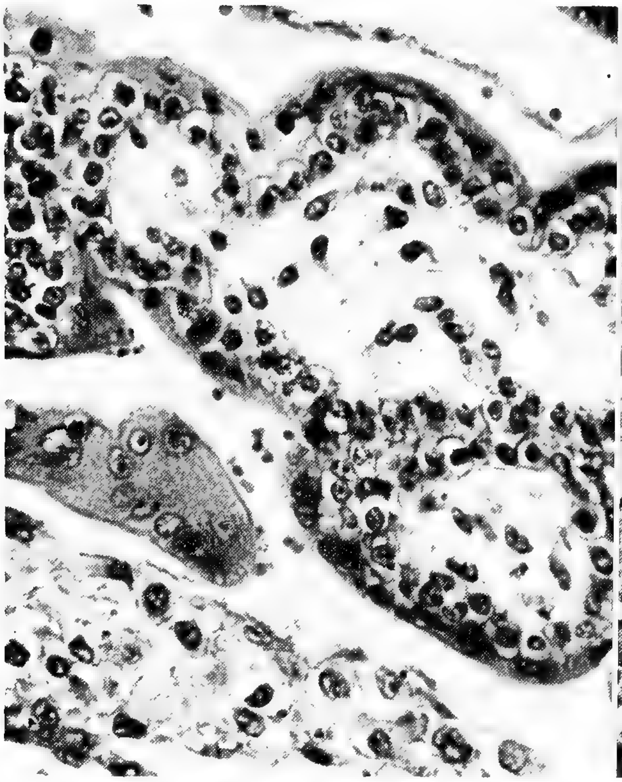


Fig. 293. Chorionic villi from a young pregnancy before the blood vessels have formed. The two layers of epithelial cells are very clearly seen. A large mass of syncytium is present in the central portion of the photograph.

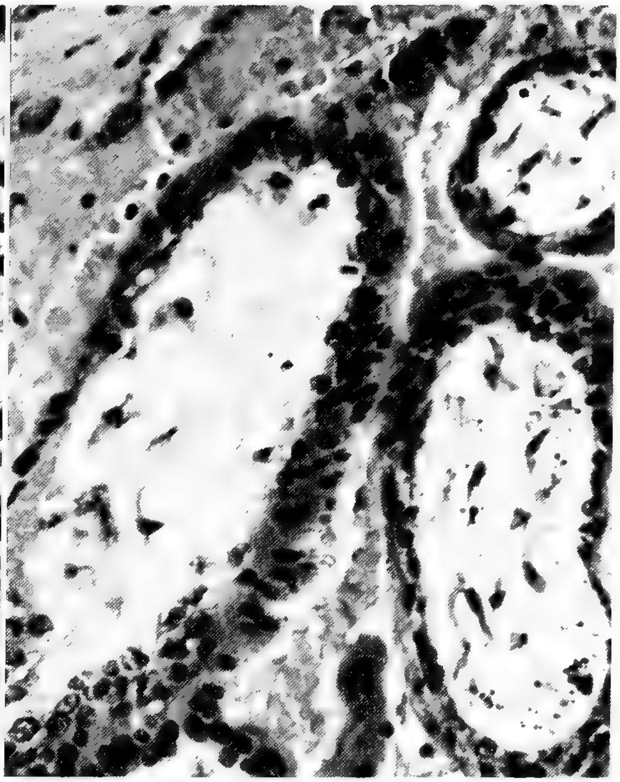


Fig. 294. Retained membranes. Villi which have been retained in the uterus from an incomplete abortion. That it was an early pregnancy is attested by the lack of blood vessels in the center. Degeneration has occurred with death of the pregnancy.

hormone has been used extremely widely in the treatment of threatened abortion. In the earlier papers, only a minute amount of progesterone, as 1/5th of a rabbit unit, was reported to improve the salvage rate for abortions greatly. Lately, large doses of progesterone have been given, as 100 mgm. daily. The numerous reports of series of cases of threatened abortion treated with progesterone with good results may be looked upon with doubt. Progesterone allays spasm and contraction in the smooth muscle of the uterus, and aids in the formation of a proper decidual bed for the embryo, so that treatment with this hormone is a very logical procedure. Yet, with further observation, it appears that a primarily irritable uterus or defect in the decidua itself rarely is a cause of abortion. This is especially evident when one compares the pregnandiol excretion values in the urine in women with threatened abortion. If the level is lower than normal, essentially all of these cases will proceed to abortion regardless of any progesterone therapy. If the level is normal, one would assume that no more progesterone is indicated. The administration of progesterone to patients with abortions that have become inevitable may prevent contraction of the uterus and extrusion of the products of conception, so that a missed abortion is produced, with retention of placenta and the embryo which has degenerated. While abortion may be complete, not infrequently abnormal bleeding follows, and curettage is necessary.

The use of estrogens in the treatment of threatened abortion was particularly popularized by Karnaky, and later by Smith and

Smith, who advised large doses of stilbestrol, a synthetic estrogen, and obtained excellent results from use of this synthetic estrogen. More critical observation recently (Ferguson) indicates that the estrogen is of little or no value for the treatment of abortion.

Of late, interest has developed in the citroflavinoids, the material obtained from the pulp of citrus fruits, which is thought to correct capillary fragility, as a possible cause of bleeding from the uterus and placental bed, and which may be a cause of threatened abortion. Small series have been reported as showing extraordinarily good results. But, after seeing the numerous good reports on treatment with progesterone and estrogen, one tends to be skeptical of this presently popular treatment.

Certain procedures are of importance in the treatment of threatened abortion, which may become an inevitable abortion, and which may possibly prevent such a sequence of events. The first is bed rest for the patient in pregnancy with uterine cramping and scant vaginal bleeding. Sedation is used as necessary, occasionally with narcotics, but more often with tranquilizers and barbiturates. With this regime, either the bleeding will stop and the cramping recede, or the chain of events will progress to an obvious inevitable abortion, which may be spontaneous and complete, or may require curettage to remove the retained placenta. A second important point in the treatment of abortion is the abstinence from sexual intercourse. It appears that in many patients, sexual intercourse in early pregnancy may cause uterine cramping and scant bleeding. If the practice is continued, undoubtedly abortion may occur in many instances. When there have been repeated abortions with previous pregnancies, or when there is threatened abortion, abstinence from sexual intercourse should continue throughout the pregnancy, certainly past the third month.

Thyroid extract is an important factor in threatened abortion, though not of value in acute bleeding. It is more important, when indicated, for the patient with repeated abortion who has a lowered basal metabolism, that thyroid extract in the proper amount be given long before the next pregnancy begins.

The strength and ability of the spermatozoa of the husband undoubtedly are equally important as the egg in fertilization. In repeated abortions, semen analysis is indicated, and not infrequently lowered sperm counts are found. Perhaps treatment in some of these instances is of value for subsequent pregnancies.

When the abortion has become inevitable but not complete, as determined by the continued bleeding, dilatation of the cervix, the presence of some of the placenta low in the cervical canal, and the occurrence of contractions, manipulation may be necessary. Often the cervix is widely dilated, the placenta and blood clots are low in the cervix, and they may be lifted out with the sponge forceps and perhaps complete the abortion very readily. However, this procedure performed outside the operating room has certain risks, although apparently slight. There may follow a profuse amount of bleeding that can be quite disconcerting. One would prefer the removal of placental tissue in the operating room with proper vision and instruments, and with facilities for combating hemorrhage by packing, fluids, and even transfusions if necessary. In the acute episode, and in the more chronic case, in which there is a history of spontaneous abortion some days or weeks or months previously, followed by prolonged and irregular bleeding, curettage is indicated. The dull curette is used, but also the sharp curette when the uterus has become firm and time has elapsed. Always, the ovum forceps, or the polyp forceps (the Randall ureteral stone forceps), are particularly advantageous in the more chronic cases, and all polypoid tissue is carefully removed.

In some instances, retained placental tissue may be present over very many months, or

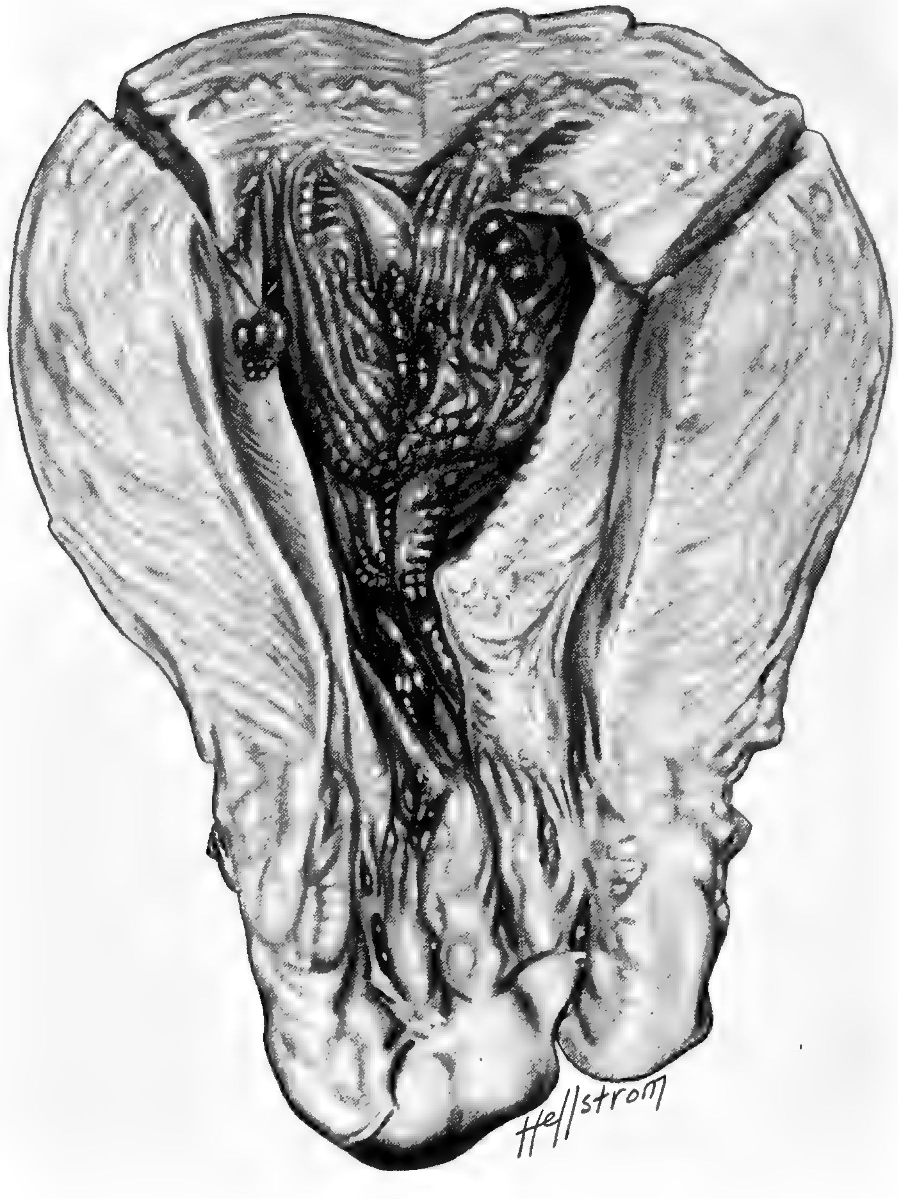


Fig. 295. Placental polyp. The portion of firmly attached placenta may have been here for many months, following an abortion or retained placenta after delivery. It is not a true polyp but has been compressed by the uterine contractions to have a polyp-like form. Usually these polyps are firmly attached, and hysterectomy may be necessary.

more than a year, particularly in the fundus, but perhaps attached to the side walls. This may have an origin in the form of localized placenta accreta, a strange situation in which the placenta seems to grow deeply into the uterine wall. When a portion of placenta has been moulded inside the uterine cavity and connected only at one end, it develops the form of a polyp, quite firm, of dark purplish, or hemorrhagic color, and granular in appear-

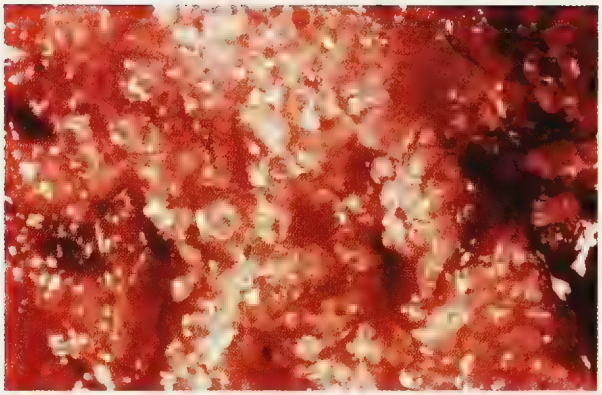


PLATE VI

Hydatidiform mole. This close-up view shows the prominent, grape-like, hydatidiform enlargement of the many villi of this placenta. Benign.

ance. This is called a placental polyp. It is not a new growth in the sense that the ordinary polyp may indicate, but is simply the moulding of attached placental tissue. These placental polyps occur more frequently when the pregnancy is more advanced, particularly in the last trimester, and following delivery.

Syncytial endometritis is found at intervals after curettage in women with abnormal and irregular bleeding, in which there is a chronic endometritis, as evidenced by the presence of lymphocytes and plasma cells in the endometrium itself, and the presence of syncytial cells remaining in the endometrium and extending somewhat into the myometrium. This has been called syncytioma, and has been mistakingly considered as related to chorionepithelioma. But syncytial endometritis is not malignant, nor premalignant, and is a form of incomplete abortion, or retained membranes with local chronic inflammation. The treatment is curettage, although on occasion the patient may not be cured of bleeding if it cannot be removed completely. Occasionally hysterectomy may be necessary. The more conservative procedure is expected to cure the majority.

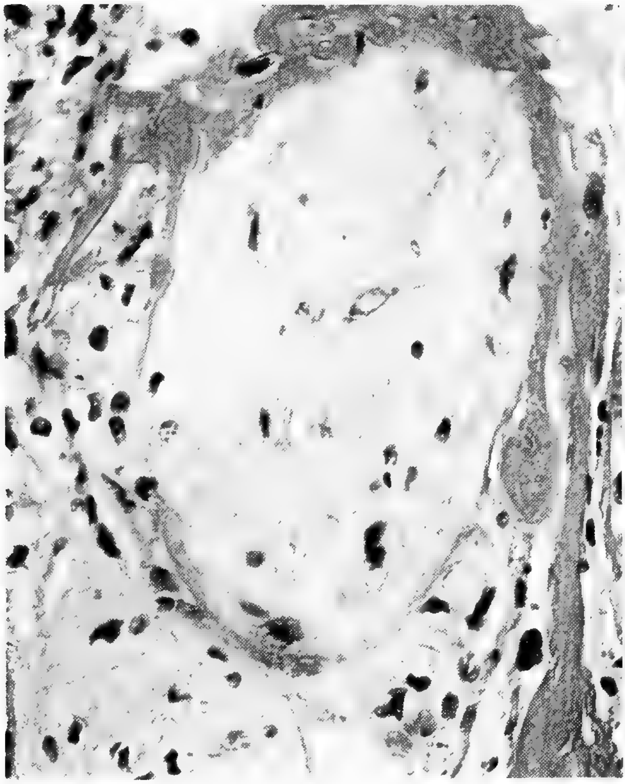


Fig. 296. Placental polyp. A portion of placental tissue has been attached for a long period of time in the fundus of the uterus. The villi are largely hyalinized due to lack of blood supply and the trophoblasts have disappeared.

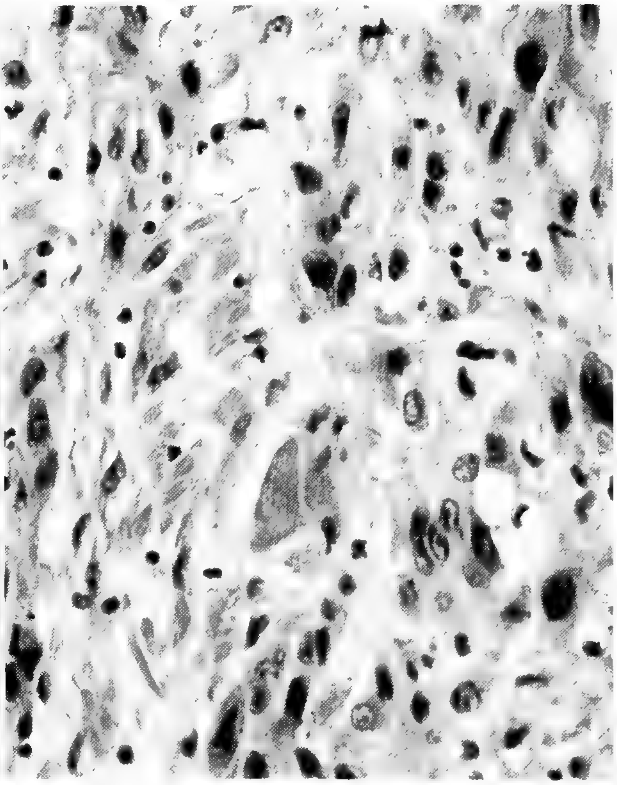


Fig. 297. Invasive trophoblast of normal pregnancy. These trophoblastic cells are mainly syncytial, but also there are some Langhan's cells. They are invading normal myometrium and do not represent malignancy. The differentiation may be difficult.

HYDATIDIFORM MOLE

Hydatidiform mole is a disease of the young placenta. It develops before the blood vessels have formed within the villi. Hydrophic swelling and liquifaction of the interior of the villi are accompanied by a marked proliferation of the trophoblasts, both the Langhan's cells and the syncytium. On the one hand, this may be considered a degenerating disease of the placenta, in that it does not proceed to normal development and is associated with a marked bulbous, grape-like swelling of the individual chorionic villi; and on the other hand, it may be considered a neoplasm, in that there is a remarkable overgrowth of the trophoblasts and a change in the cells so that they appear to be growing quite abnormally.

The hydatidiform mole is said to occur in one in 2500 pregnancies. It is most obvious in the complete form, in which essentially all of the villi are involved in this marked hydrophic swelling. In these complete hydatidiform moles, the embryo and fetus cannot develop because of the absence of the establishment of any circulation in the villi, and the embryo or young fetus disappears rapidly and completely. In the partial hydatidiform mole, in which a varying proportion of the placenta may be involved, there may develop, in the remaining normal placenta, blood vessels that function sufficiently to nourish a normal fetus. A normal delivery of a living infant may follow.

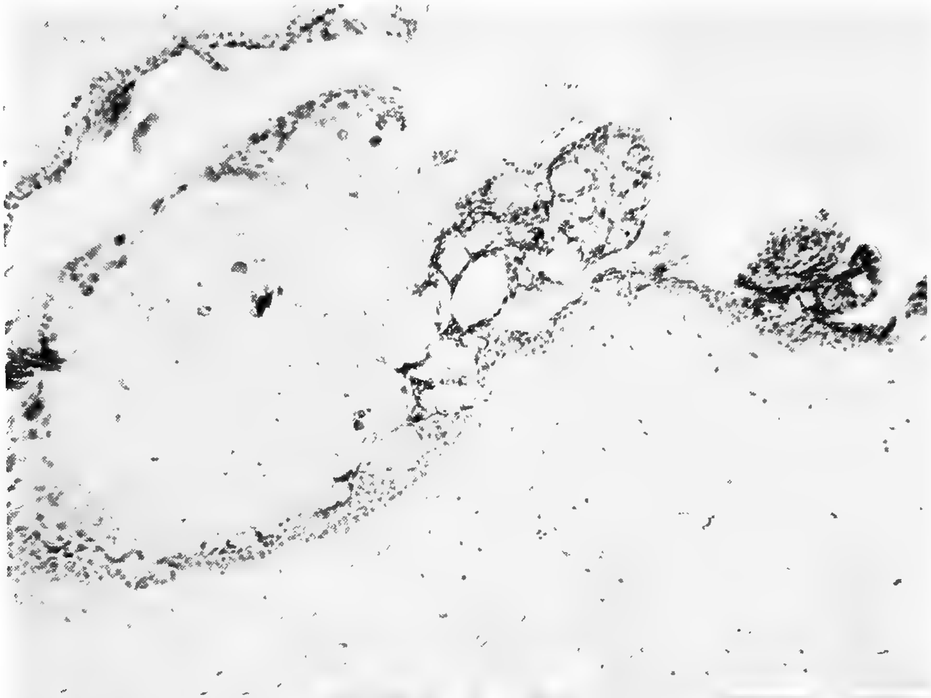
Great interest has been directed to this change in the placenta, and the related chorioma destruens and chorionepithelioma, to be elaborated on further in this chapter. Marchand, in 1895, made excellent descriptions and summaries of these diseases. In modern times, the great gynecologic pathologist, Emil Novak, had many publications on these subjects. Because of his interest, he supervised the *Matheu Chorionepithelioma Registry,* established by the American Gynecological Society. The further publications of Hertig, and the hormone studies from the time of Zondeck in 1929 to those of Delfs in 1957, in addition to the numerous other investigators and individual case reports, have added much information regarding these diseases.

In the first trimester of pregnancy, the young placenta is characterized by a marked growth and proliferation of the Langhan's cells and the syncytium, particularly the former, which are responsible for the production of the chorionic gonadatrophin, which appears in quite large amounts when the pregnancy is of six to seven weeks of age. Not only is there proliferation of this young epithelium under normal conditions, but it tends to invade the uterine wall in degree, although the uterine wall is protected rather well by the basalis of the endometrium. These embryonic cells tend to invade blood vessels, carrying with them complete forms of the young villi, which break off in the blood vessels and metastasize to the lungs, and undoubtedly to other areas in the body. These invading and metastasizing trophoblastic cells may appear malignant in their normal growth. Perhaps these metastasizing cells may remain in some areas to become the seat of malignant tumors in later years, but more often they become lysed and disappear. This latter idea remains a speculation. At any rate, the proliferation of trophoblast occur in much greater degree with the hydatidiform mole than with normal pregnancy, and is associated with marked abnormalities of the nuclei of both the Langhan's and syncytial cells, as to appear quite malignant.

Hydatidiform moles are followed by the development of the malignant chorionepithelioma in about three per cent of the cases. Because of this occurrence, the follow-up of the hydatidiform mole is of the gravest importance.

The symptoms of the mole are primarily that of bleeding in early pregnancy. Most cases with bleeding in early pregnancy have threatened abortions, or inevitable abortions, or completed abortions, and are to be handled in a conservative manner, with observation on the one hand, interference by curettage when necessary, and further observation when spontaneous and apparently complete. The symptoms of the mole are not distinctive in their early stage. The mole produces a minor problem in practice as regards occurrence, because

Fig. 298. Hydatidiform mole of typical appearance. Huge villi, with liquified centers and myxomatous cells around the border, have a surface epithelium of very hyperplastic Langhan's cells and syncytium.



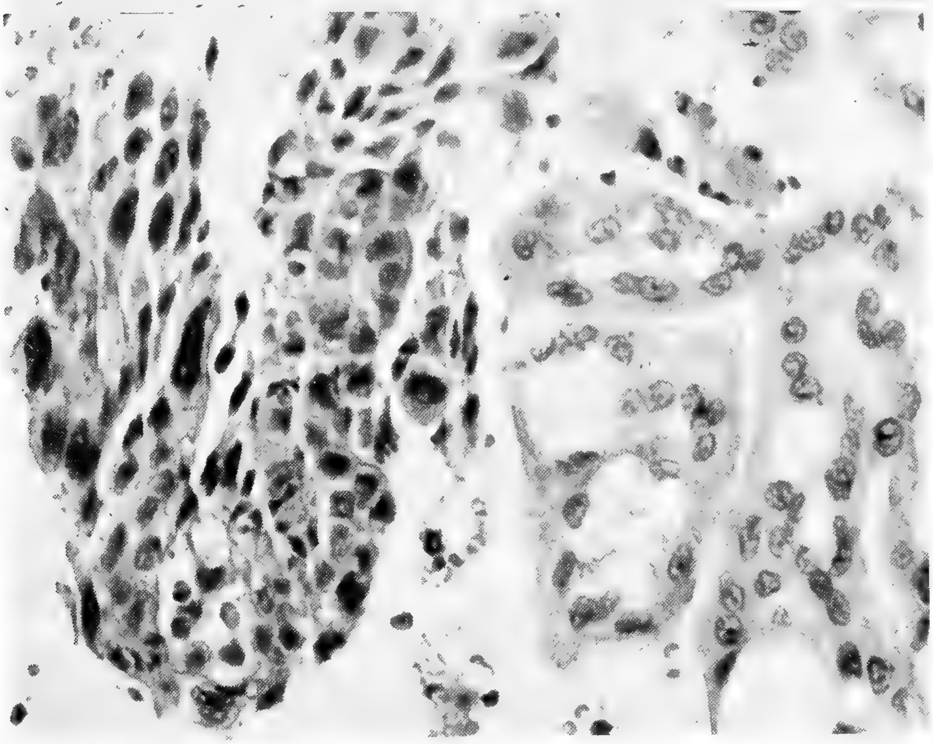


Fig. 299. Hydatidiform mole, high power view showing marked proliferation of syncytium and Langhan's cells. The villus is not shown.

abortion is the frequent abnormality of early pregnancy. The symptoms invariably begin in the first trimester, but may be continued into the second trimester before the diagnosis is made.

The diagnosis of the hydatidiform mole may be exceedingly difficult, because the differentiation from early threatened abortion is impossible on clinical examination. After sufficient time (a few weeks), because of the individual enlargement of the tiny villi to many times their normal size in a relatively short period of time, the entire volume of the placenta increases in size causing the uterus to enlarge rapidly and to a greater degree than normal pregnancy of that age. This usually is confusing, as the variation in the size of the uterus in early pregnancy may show remarkable change from one examination to the next, on the one occasion the uterus being contracted and firm, and on the next being quite soft, relaxed, flabby, and larger, and yet normal. Also, there may occur with multiple pregnancies, as with twins, a much larger uterus in early pregnancy than the average normal. The diagnosis is really clinched when the examination reveals a grape-like structure, or more than one, appearing from the cervical os, or in the vagina, or when the patient has noted the passage of these bulbous villi. On the other hand, one might suspect the possibility of a hydatidiform mole and attempt to use the chorionic gonadatrophin test to distinguish the presence of a mole. This may be determined by the quantitative studies of excretion of chorionic gonadotrophin either in the urine or in the blood serum. Delfs has indicated that the serum determinations are more accurate, and that the gonadotrophin in the twenty-four hour specimen of urine may be destroyed in degree over the duration of time in collection of the specimen. Another difficulty is that at the age of six or seven weeks of normal pregnancy, the production of chorionic gonadotrophin by the proliferated Langhan's cells may reach an astronomical amount, namely, six hundred to seven hundred thousand units per liter of serum in one normal case, or on fifty thousand units per liter of serum in the next normal case. The continued formation of these large amounts of chorionic gonadotrophin is suggestive evidence of the presence of the hydatidiform mole, because the level ordinarily drops very rapidly to ten to twenty thousand international units per liter of serum by the eighth or tenth week of pregnancy, and may reach a much lower level than this in the remaining months of pregnancy. Varying tests of the gonadotrophin in the urine by the Friedman-Lapham rabbit test, or the Aschheim-Zondek mouse test, or the various male or female frog tests, have been offered as quantitative methods for the determination of chorionic gonadotrophin, but the variation of the normal has caused much confusion in many cases. More often the diagnosis will be made by the eventual findings of the hydatid, which is passed through the cervix into the vagina, but this proof may be delayed sometimes for a distressing period. Often, the mole is extruded as an abortion, which clarifies the diagnosis.

The treatment is dependent on a diagnosis, which, as stated, usually depends on finding the aborted mole, which is obvious. The important point after this is the possible development of a chorionepithelioma following the passage of the mole. For this reason, as a rule the patient who has passed the mole usually is curetted a week or two following the abortion, or six weeks later.

The hydatidiform mole is of itself a benign disease. Regardless of the degree of cellular atypia that may occur, it appears that malignancy cannot be diagnosed from the examination of the curettings from the uterus. Also, it would appear that the benign, invasive mole, to be elaborated upon further, cannot be distinguished in a microscopic examination of the involved villus. An important part of the treatment is the follow-up of the hydatidiform mole, because chorionepithelioma may develop subsequently in these cases. Obviously, some of the molar tissue must have remained in the uterus, if a subsequent tumor is to develop. For this reason, the original curettage, after expulsion of the mole, whether immediately, or more often a week or six weeks later, is of much importance. After this, the patient should be followed with tests for chorionic gonadotrophin, usually to be performed as the ordinary pregnancy test. The patient must be cautioned not to be exposed to pregnancy during this period of follow-up. The tests are repeated at bimonthly or monthly intervals for three or four months, and then at further intervals for a year or two years. If the test becomes positive, one must assume that molar tissue has remained in the uterus, and that a possible chorionepithelioma has developed. Curettage is repeated. If the pregnancy tests continue to be positive subsequently, hysterectomy is considered. In women who have had several children, primary hysterectomy is to be considered, because of the risk of malignancy in the three per cent of cases. Every effort is made to save the uterus as a rule, but there are practical reasons to indicate more extensive therapy in certain cases.

Associated with the hydatidiform mole are

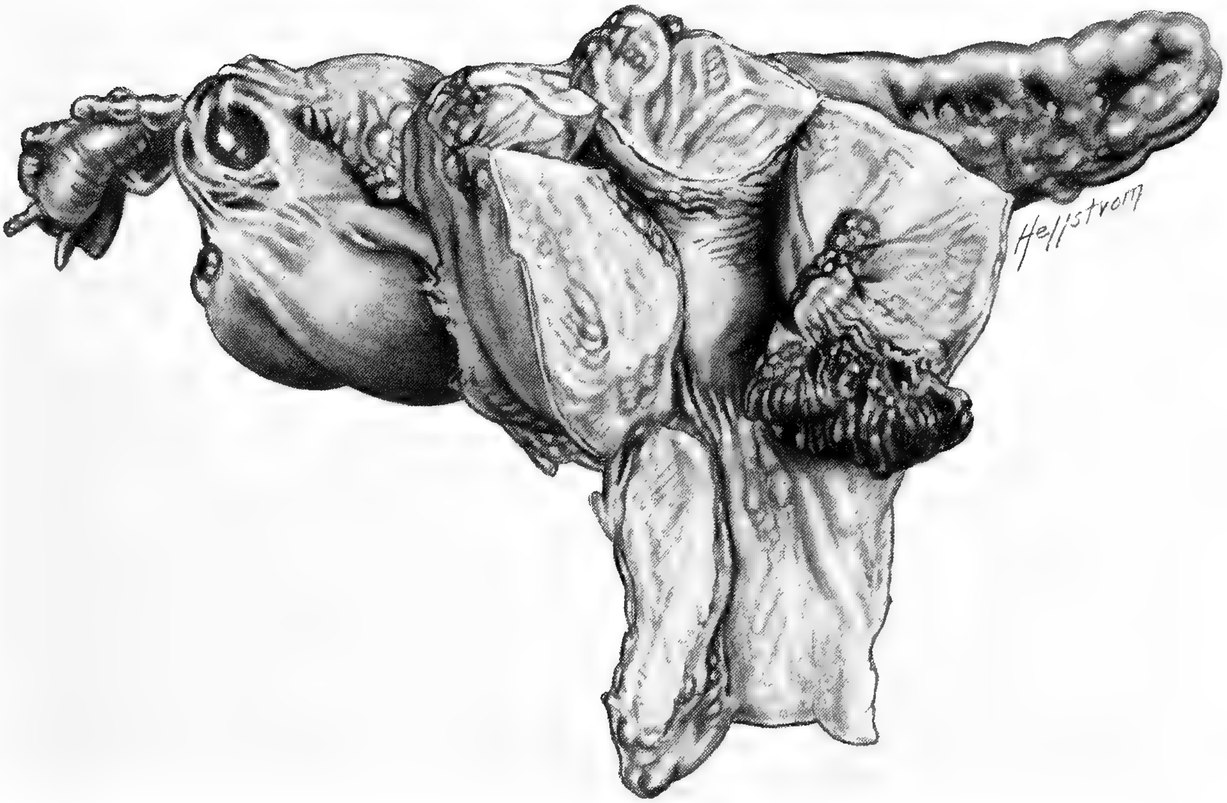


Fig. 300. Chorioma destruens, invasive hydatidiform mole. This twenty-three year old patient had a large mole, the size of a seven months pregnancy, removed by Caesarian section. At the same time theca lutein cysts were resected. Subsequently pregnancy tests continued positive, although two curettages removed small portions of moles. Because of persistent positive tests, bleeding, and suspicious cells in curettings, hysterectomy was performed. Deep in the muscularis, almost perforating the uterus, were found benign hydatidiform villi. For the next twelve years, patient has remained well.

changes in the ovaries, caused by the very large amount of chorionic gonadotrophin, or perhaps other unknown hormone stimulation. These changes are lutinization of the thecal cells surrounding the follicles. This luteinizing effect, which may be quite marked and may cause the development of large and multiple thecal lutein cysts in the ovaries, five to twenty cm, in diameter. Probably about fifty percent of cases with hydatidiform mole develop palpable thecal lutein cysts; in the remainder, the ovaries are not clinically enlarged. These similar thecal cell changes occur with the invasive mole and the chorionepithelioma. It is of interest to know that if all of the molar tissue has been removed that the cysts should recede and the ovary become normal again. If the ovaries remain enlarged, in spite of one or two thorough and careful curettages of the uterus, then one must conclude that further mole tissue remains present, or that a chorion epithelioma has developed. In other words, in these cases the persistence of the ovarian cysts after conservative procedures, indicates a more radical approach.

CHORIOMA DESTRUENS

The invasive hydatidiform mole, or the benign, metastasizing hydatidiform mole, is distinguished as a separate entity under the term, chorioma destruens. In these relatively uncommon cases, the chorionic villi of the mole invade the wall of the uterus, perhaps in large and diffuse areas, and destroy muscle tissue and cause hemorrhage locally. The chorioma destruens may follow a pregnancy after a considerable period of time. The invasive mole must always begin as an ordinary hydatidiform mole, which becomes invasive in its inception, or much later from small fragments of mole which may remain in the endometrial cavity. In some instances of recurrent positive pregnancy tests, following a hydatidiform mole, and following repeated curettage, invasion of hydatidiform mole in the myometrium has been found, which has been impossible to remove by curettage. The invasive mole tends to extend through the uterine wall and the peritoneal surface of the uterus, and if large blood vessels are in that area, as on the lateral sides of the uterus where the uterine vessels penetrate the uterus, severe and fatal hemorrhage may occur. The symptoms are those of ectopic pregnancy, with a history of missed menses, abnormal bleeding, and possible abortion. If hemorrhage, with severe and acute symptoms, does not develop, infection possibly follows, which may cause complicated lesions in the pelvis, with tubo-ovarian abscess and parametritis. On the other hand, the mole may grow out into the pelvis, form masses of molar tissue, and invade the surrounding structures. Still, this is called a benign, but invasive

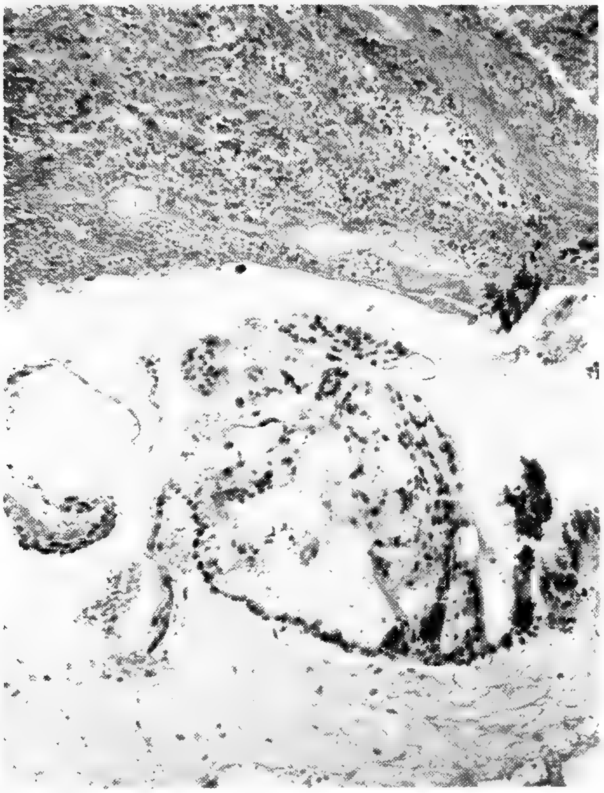


Fig. 301. Chorioma destruens, showing proliferation of trophoblasts on the mole, with marked coagulation necrosis adjacent to it.

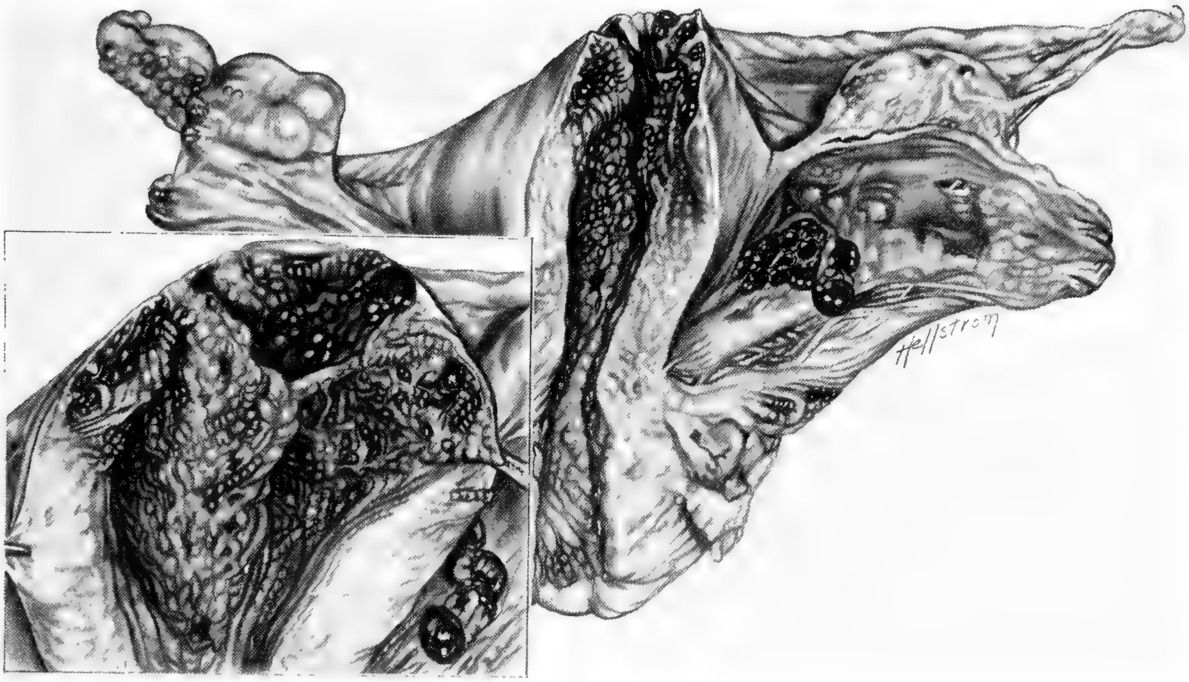


Fig. 302. Chorioma destruens. Age nineteen years. Patient was thought to have had a spontaneous abortion. She died of intra-abdominal hemorrhage from the perforation below the right ovary which involved the uterine artery. The small hydatid forms are seen in the uterine cavity and invading the muscularis extensively. Only prompt hysterectomy could have saved her, if the diagnosis had been realized.

hydatidiform mole. There are well defined villi, or a molar type, without the tendency to metastasis and early death, as with the chorionepithelioma.

In occasional instances, there have been reported cases of metastases from the chorioma destruens to the lungs, or other areas of the body, with the formation of tumor masses composed of hydatidiform mole tissue. Delfs has reported one particularly interesting case, with metastasis to the spine, repeated excision, and finally irradiation therapy. After several recurrences, death followed. More often, this form of the mole remains entirely local in the myometrium, and in adjacent areas in the pelvis, if it has perforated the serosa of the uterus.

In these cases, the chorionic gonadotrophin usually remains at a high level, although varying in degree, and perhaps dropping to relatively low levels at times. There are reported instances in which the gonadotrophin has returned to normal without treatment; apparently there has been absorption of the chorioma destruens, even in its metastases.

The symptoms of this form of placental disease are similar to those with the hydatidiform mole, usually being associated with early pregnancy, following the apparently benign hydatidiform mole, or following a normal pregnancy.

The diagnosis might be assumed if curettage removes no tissue, and there remains a high titer of chorionic gonadotrophin or even an ordinary repeatedly positive pregnancy test. It would be difficult to distinguish an invasive chorion-epithelioma. The diagnosis really is made after hysterectomy. The excised specimen may show obvious invasion, or molar tissue may be seen out in the pelvis and around the uterus. When a mole occurs outside the uterus, the possibility of origin from an ectopic pregnancy, and not an intrauterine lesion, must be considered. A study of the gross and microscopic specimen may confirm the diagnosis in a particular case. All local tumor should be excised, if possible. If the ovaries are not involved, they are not removed. If there are metastases, excision may be attempted. Irradiation therapy, androgens and chemotherapy may be tried.

CHORION EPITHELIOMA

Chorion-epithelioma, chorio-carcinoma, or chorioma, is a malignant growth, involving the trophoblast, the Langhan's cells and the syncytial cells. As a rule, both of these cells are involved in the invasive tumor, although the Langhan's cells seem to predominate, sometimes almost completely. Unless some syncytium can be found, the diagnosis may be extremely difficult. This malignant epithelioma, without any villi accompanying its invasion, extends into the wall of the uterus and causes marked necrosis of the muscle tissue, so that there is characteristically formed a coagulation necrosis about the advancing tumor. The malignant cells invade into blood vessels, and metastasize very early. Hemorrhage commonly occurs about the tumor. Almost never are any villi found associated with a chorion-epithelioma, and certainly not in the invasive part of the tumor below the surface of the endometrium. Novak has indicated that forty per cent of the cases follow hydatidiform mole, forty per cent follow incomplete abortions, and twenty per cent follow term deliveries of apparently normal pregnancies.

Cellular atypia, hyperchromatism, and mitosis in the invading tumor cells, may be most frequent, or no more marked than that in the normal pregnancy, or in the hydatidiform mole. The changes in the individual cells are not particularly diagnostic; the cell changes are not as important as the invasion of the masses of cells, with accompanying coagulation necrosis, hemorrhage, and the absence of accompanying villi.

The symptoms of the chorion-epithelioma are very difficult to determine. If the patient has had hydatidiform mole, and bleeding continues, and the pregnancy tests are positive in spite of repeated curettage, one must assume the presence of either chorioma destruens or chorion-epithelioma. While it has frequently been said that the amount of chorionic gonadotrophin is much increased with the chorion-epithelioma, and some have indicated that the diagnosis may be made with this method, as a rule the difference in amount of the chorionic gonadotrophin is not sufficient or

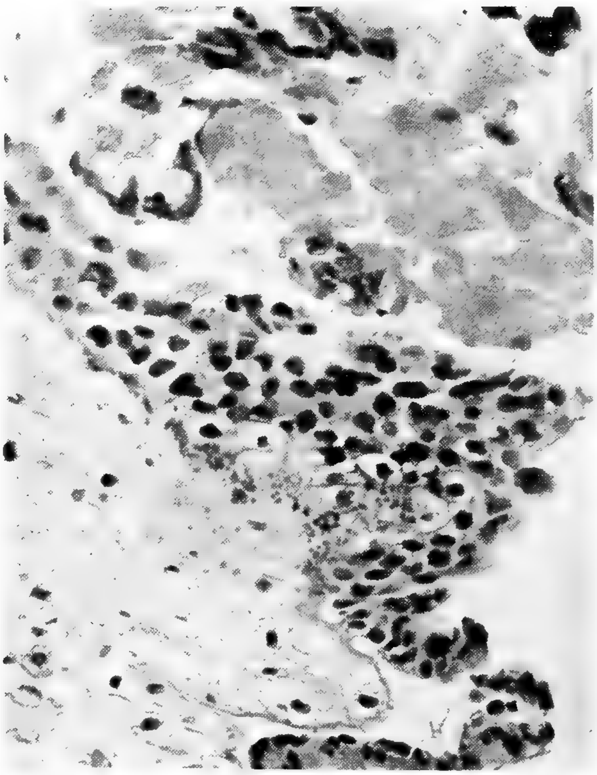


Fig. 303. Chorioma destruens, showing marked proliferation of Langhan's cells and coagulation necrosis adjoining the invading molar villus.

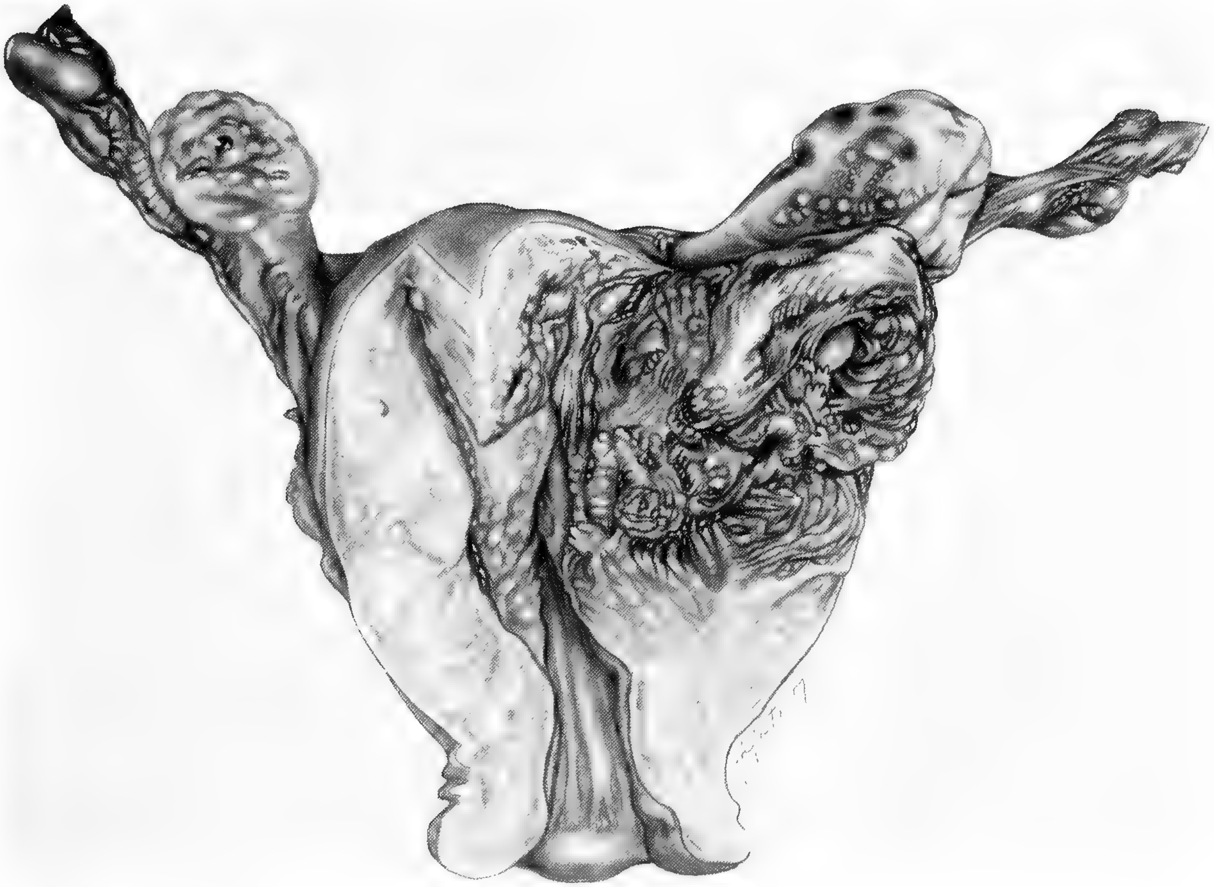


Fig. 304. Chorion-epithelioma. A malignant tumor extending through the myometrium. Patient had normal delivery three months previously, followed by irregular bleeding. Purplish-red tumor nodule on vaginal wall was first suggestion of diagnosis. Biopsy of vagina showed chorion-epithelioma. Because hysterectomy and bilateral salpingo-oophorectomy are sometimes followed by remission of other metastases, this operation was performed. Patient died one month later with generalized metastases.

invariably increased enough to allow distinction between the hydatidiform mole and the malignant tumor. If the patient has no history of a mole, then she may have a history of abortion with continued bleeding over a period of time, perhaps even several months. If this malignant disease follows a term delivery, irregular bleeding may be produced. The diagnosis may be evident by the finding of a bluish mulberry tumor nodule in the vagina or on the vulva; these appear frequently to indicate one of the earliest areas of metastasis. In other cases, the patient may develop a cough, and x-ray films of the chest may show metastasis to the lungs. Patients with this disease become rapidly ill, tend to hemorrhage increasingly from the uterus, and succumb in a matter of a few weeks, or certainly in a very few months.

The treatment of chorion-epithelioma is most discouraging. Usually, the diagnosis is made too late in the disease. As a rule, conclusion cannot be made from the curettings, although, in rare instances, such a diagnosis may be made. Always the diagnosis is presumptive. If cure is to be obtained, excision must be performed relatively early. The very rarity of the disease makes the odds small that malignancy will follow in an individual case. However, if repeated curettage after a mole is followed by continued positive pregnancy tests, hysterectomy may prevent and cure some of these cases in an early stage. As a rule, the patient with metastases will not be cured by operation.

However, this is a strange disease, undoubtedly related greatly to hormones. There are reported cases of spontaneous cure without treatment, and there are reported cases of regression of the metastases after hysterectomy and bilateral salpingo-oophorectomy. It does appear that the latter operation is indicated, even in the presence of metastases. The cure of patients with mothball lesions in the chest after a curettage for mole, after hysterectomy, after lobectomy, after irradiation therapy, after chemotherapy, or even after observation and no treatment, makes it clear that the modus operandi of this disease is different from the usual malignancy.

The history of chorion-epithelioma is a dramatic one; the disease is, as a rule, devastating. Obviously it has a strong relation to the hormones; and when the key to the latter is obtained, the secret of this strange malignancy may be unfolded.

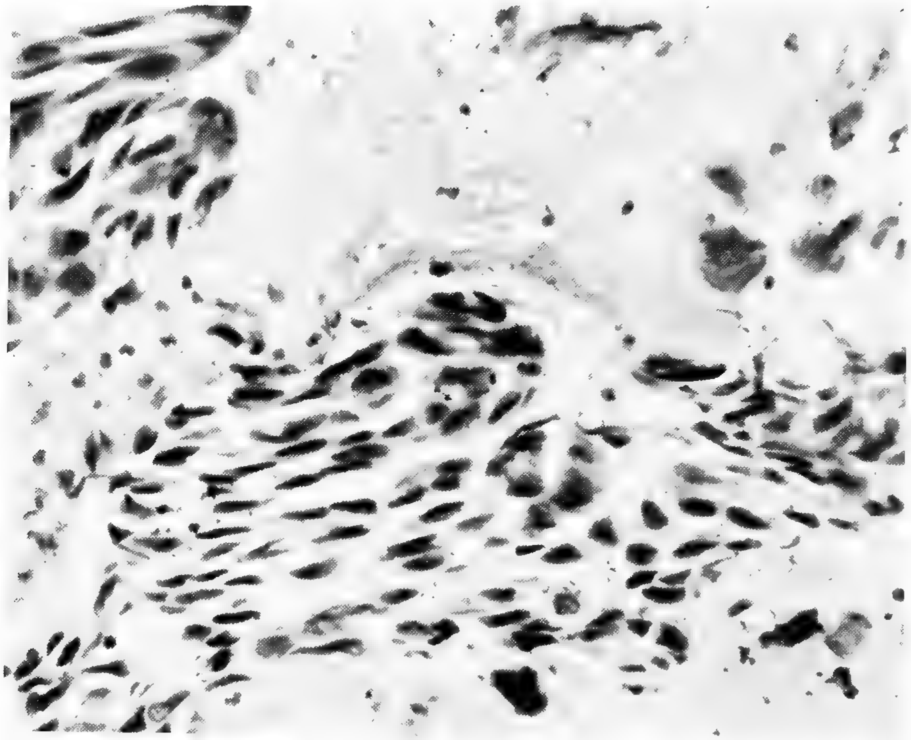


Fig. 305. Chorion-epithelioma (chorio-carcinoma, chorioma). The invading Langhan's and syncytial cells are flattened and elongated here. Almost all of the nuclei show pyknosis and abnormal forms. The coagulation necrosis about the masses of tumor cells has long been considered a diagnostic point. Note absence of any villous forms in the invading and metastatic areas.

DISEASES OF THE PLACENTA AND PREGNANCY IN THE MID-TRIMESTER

In the mid-trimester of pregnancy, the main pathological process is miscarriage, the causes of which are completely unclear. As a rule, the fetus is normal. Possibly, the cause of mid-trimester abortion lies in a hormone defect. Possibly psychogenic effects, with disturbances of the autonomic nervous system, resulting from tensions and anxieties, fears and emotional confusion, may cause some of these late abortions. A goodly number have been ascribed to the incompetent cervical os, a congenital abnormality in the muscles closing the cervical os, a defect caused by operative procedures, (even dilatation and curettage have been implicated), a relaxation caused by hormone deficiency, the nature of which is not understood, or an incompetence caused by trauma and disruption of muscle fibers of the lower uterine segment from previous delivery. The latter seems important as a cause of the incompetent os. Lash, who has developed various operative procedures, treats the incompetent os in the non-gravid patient by removing wedges of tissue from the cervix. When seen during pregnancy, in the fifth to eighth month, Shirodkar has advised the insertion of straps of various fascias around the cervical os. This has been developed in this country by Barter, Riva, and others, so that the strap procedures (now with plastics) have become quite popular at this time.

PLACENTAL DISEASES IN LATE PREGNANCY

Other changes related to late pregnancy are found in the placenta. Erythroblastosis is associated with fibrosis and slight enlargement of the villi, somewhat similar to the change occurring with congenital syphilis of the placenta. Other diseases of the placenta in late pregnancy include the angiomas of varying size and degree, which are not infrequent, and apparently of no clinical importance. The nature of the infarcts of the placenta are

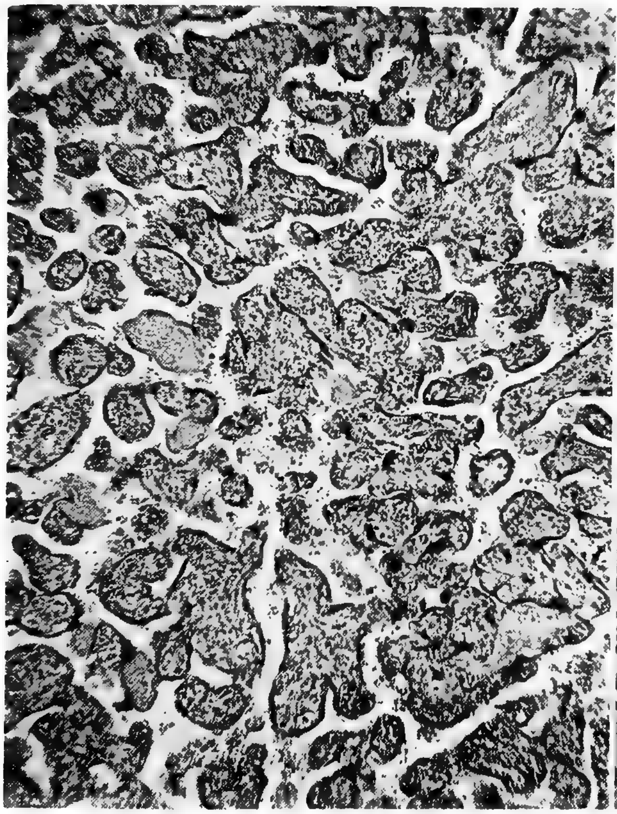


Fig. 306. Normal placenta at term. Note the villi are quite small. Varying degrees of arteriosclerosis has occurred and the surface epithelium is almost entirely that of syncytium, the Langhan's cells having disappeared.

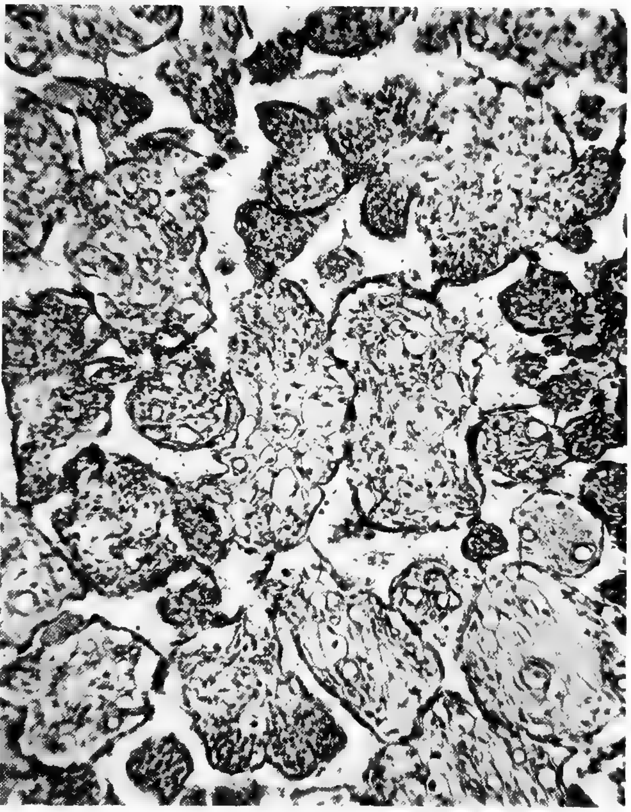


Fig. 307. Placenta of erthyroblastosis. Note that the villi are quite enlarged, fibrous appearing, have multiple minute blood vessels. Within many there may be seen nucleated red cells in clumps.

not clearly understood; they have been related by some (Bartholomew) to toxemias of pregnancy. Others have seen no distinct relation to any disease.

Since the diseases of middle and late pregnancy belong primarily to the science of obstetrics, they will not be elaborated upon further in this area.

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CHAPTER XIII

Hermaphroditism and Congenital Anomalies

HERMAPHRODITISM

Hermaphroditos was the two-formed progeny of Hermes and Aphrodite. According to Ovid, this body could not be called woman or man, but seemed neither and yet both. Since the time of the great poets and philosophers, this form of the human body has been of great interest to artists, including poets, painters, and sculptors, and also to physicians and scientists, including the embryologists, obstetricians, and gynecologists, psychologists, and pediatricians.

The first and most important classification of hermaphroditism was presented by Klebs in 1876, who determined that the true hermaphrodite (hermaphroditismus verus) must contain within the body both ovarian tissue and testicular tissue, as proved by microscopic examination. This might occur in the form of a separate ovary and a separate testis on opposite sides, or with the formation of an ovotestis, with both ovarian tissue and testicular tissue in one side, with a normal gonad of either sex on the other side, but the individual must have both tissues present. Klebs suggested sixteen subdivisions of true hermaphroditism.

Then, Klebs said the remainder of cases, and the great majority, should be called pseudohermaphrodites. The male pseudohermaphrodite contains testes but varying degrees of the female form of the external or internal genitalia. The female pseudohermaphrodite contains ovaries but varying forms of masculine external or internal genitalia. A number of cases, representing subdivisions or combinations and variations, documented each type of pseudohermaphroditism, but the main subdivisions were pseudohermaphroditismus completus, pseudohermaphroditismus internus, and pseudohermaphroditismus externus.

In 1937, H. H. Young published his book *Congenital Anomalies, Hermaphroditism, and Related Adrenal Diseases,* already considered a classic and a collector's item. Young, the great urologist, summarized all of the cases of hermaphroditism in the literature and essentially followed the classification of Klebs. His masterful surgical techniques, developed for improving genital abnormalities, were illustrated in detail.

But now, in the past ten years, or slightly more, extraordinary new developments have occurred in research in embryology and endocrinology, so that an entirely new concept has developed. This is based particularly on the work of the great French embryologist, Alfed Jost, and has been especially applied to clinical use by the pediatrician, Lawson Wilkins, and finally has been summarized and elaborated upon in detail in H. W. Jones', Jr., and W. W. Scott's new book, *Hermaphroditism, Genital Anomalies and Related Endocrine Disorders* (1958).

With the correlation of the research of many investigators in the very recent past, Jost has summarized, with the addition of his own brilliant investigations in the rabbit, the theoretical basis for a new concept of sex anomalies. First, sex is divided into three types: (1) chromosomal sex (genetic sex); (2) gonadal sex (germinal sex); and (3) body sex (somatic sex). In the normally developed individual, these three forms are all in agree-ment. However in varying forms of sexual abnormality, or hermaphroditism, there are disagreements in the male and female forms of one or more of these segments of sex.

CHROMOSOMAL SEX

There are twenty-three pairs of chromosomes in the somatic cells (formerly there were thought to be twenty-four). Twenty-two pair are autosomes, and one pair are sex chromosomes, being either XX and of female chromosomal sex, or XY and representing male chromosomal sex. In the germ cells there are also twenty-three pairs, which are reduced in maturation to twenty-three single chromosomes. In the spermatozoa there is the sex determining chromosome, either X for female, or Y for male. When the sperm joins the egg, twenty-three pair are formed, one pair being XX, if a chromosomal female is to be formed, and one pair XY, if a chromosomal male. Recently Tjio and Puck (1958) have demonstrated beautiful photographs of the human chromosomes by special stains of cells from tissue cultures. They demonstrated forty-one large chromosomes and five small chromosomes in the male (one of the small ones represents the Y chromosome), and forty-two large chromosomes and four small chromosomes in the female (similar to the male, but lacking one small one).

The sex chromosomes can be seen in various tissues of the body, better in testicular cells in the adult individual, and also it may be seen in human dermal cells when grown in tissue culture. The presence or absence of the Y chromosome has been used in several instances in determining the chromosomal sex of human hermaphrodites, but the technique is difficult and is not practical for ordinary use. In various experimental animals, this chromosomal sex study has been extended to a great degree. Barr, and associates, in 1950, first determined the chromosomal sex of an animal by studying the morphology of nerve nuclei in the brain. Shortly thereafter this was extended to studies of the skin, and later to vaginal smears, buccal smears, and to routine blood smears (Davidson and Smith). The most practical methods of the moment include the buccal smear, which is stained with the Papanicolaou technique and studied under the oil immersion lens. Within the nuclei of the cells in females a very distinct mass of round or biconvex chromatin is found at some point near the membrane of the nucleus, deeply staining and obvious. This chromatin mass is present in at least fifty per cent of the cells of the chromosomal female. As a rule, it is present in only three per cent or four per cent of nuclei in the chromosomal male, although it may be found in up to ten per cent of the nuclei from chromosomal males. In the blood smear, which is also a very practical method of study, the presence of drumsticks attached to the nuclei of polymorphonuclear leukocytes is found in an appreciable percentage of females and rarely in males.

These new methods of determining chromosomal sex have been used widely throughout

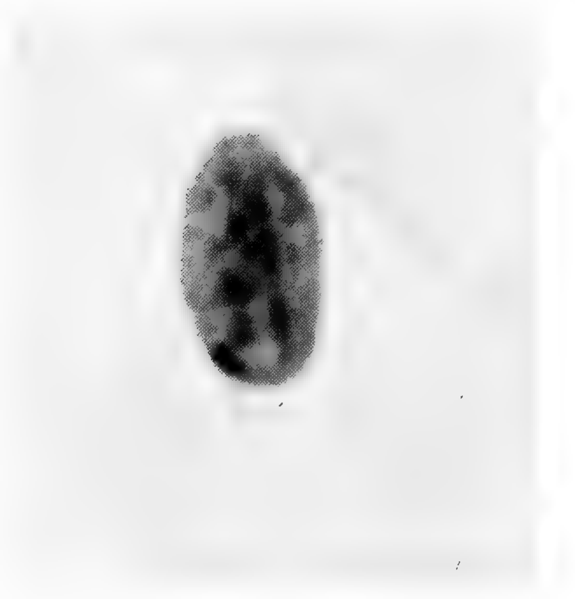

Fig. 308. Female chromosomal mass on nuclear membrane. These masses may be difficult to distinguish under the oil-immersion lens.

the world and are confirmed, but have proven confusing to many physicians. Young women with primary amenorrhea, who tend to be somewhat small of stature, with underdeveloped breasts and genitalia, with only a small amount of genital hair, but who are otherwise very obvious females in every respect, commonly prove to have the male chromosomal sex. The fact that these young women are psychologically females, that they may be developed remarkably with estrogenic hormone, and may menstruate from substitution hormone therapy, and that they may be perfectly happy wives with normal sex response, has confused most of us. But the following new elucidation of Jost, of Wilkins, of Jones and Scott, and many other investigators of the past decade, have brought an extraordinary new understanding of these problems.

GONADAL SEX (GERMINAL SEX) AND BODY SEX (SOMATIC SEX)

The gonadal sex (germinal sex) is sexual differentiation of the gonads to form either a testis with spermatazoa, or ovary with ova. The body sex includes the formation of the internal and external genitalia of the normal male or female sex.

At the time of fertilization of the egg, the chromosomal sex is determined to be either male or female. The first appearance of the early gonad in the embryo is at about three weeks of age, when it forms an indifferent mass of cells on the dorsal portion of the coelomic cavity. The germ cells come from the endodermic wall of the primitive gut. They must migrate from this gut over to the genital ridge. When the embryo is about six weeks of age, a testicular differentiation begins. The medulla, which forms much the greater part of the sex ridge at this time, contains blastema cells, more or less distinctly organized as cords radiating out toward the cortex. The cortex forms as a layer of stratified coelomic epithelium which contains scattered germ cells. This cortex is the ovarian portion of the gonad. The cords nearest the thickened coelomic epithelium or cortex contain germ cells, and constitute the primary sex cords. At about six weeks of age, the gonad may become stimulated to become a testis, perhaps from a hormonal effect of the relatively large adrenal gland. The seminiferous tubules become more prominent, and the cortex tends to recede.

The ovary develops from the indifferent gonad much more slowly and over a longer period of time. The main feature is an increase in the thickness of the coelomic epithelial or cortical cells to form a cortex. There are cortical sex cords, continuous with the primary sex cords, which press into the gonad, and later are to become the granulosal cells and germ cells. The medullary cords become smaller and compressed into the central portion of the ovary. Persistence of these medullary cords in the adult ovary may be the origin of arrhenoblastomas.

Many embryologists and experimental physiologists have added to our present knowledge from their study of amphibians, avians and various mammals, including particularly the rabbit by Jost. First, the germ cells from the hind gut migrate to the outer surface of the indifferent gonad, where they remain in the surface cells, which are to form the cortex of an ovary. Finally, they may become ova, but if there is to be formed a testicle, these same primary gonadal cells are drawn into the medulla and become spermatazoa, regardless of their genetic sex, as the somatic parts of the gonads are sex inductors for the germ cells. From this point on, either the cortex of the gonad is to dominate with the formation of the female genitalia, including the formation of ova, or the medulla is to dominate the individual and male genital organs are to be formed, including spermatazoa. In this early stage of embryonic life, an antagonism exists between the cortex and medulla, usually with complete dominance of one over the other, but varying degrees of dominance of one over the other can occur with the subsequent formation of varying sexual abnormalities.

What causes this stimulation of either the medulla or cortex at this extremely early age of embryonic life is not clear, but certainly it does appear that once the cortex or medulla is established in dominance, that some form of chemical hormone must be formed to affect the remainder of the sexual apparatus. Very possibly this theoretical hormone differs from the testosterone or estradiol produced from the adult gonad. After the cortex, or the medulla, has become dominant, with the formation of an early ovary, or early testicle, some stimulation may occur to the inactive medulla or cortex, as the opposite may be, and cause some opposing masculinization or feminization, which may affect great changes in the mullerian duct structures or wolffian duct structures, since these secondary sex structures develop much later than does the gonad itself. For instance, a very young testicle may lose its stimulating power, and atrophy to a marked degree, after which the neuter individual develops along a feminine line. That is, the mullerian ducts proliferate and form tubes, uterus, cervix and vagina, and the urogenital sinus forms female external genitalia. This is proved in experimental animals and seems to be borne out in humans, in the gonadal agenesis or dysgenesis, best typified by the young girl with primary amenorrhea and prepubertal female sexual development, appearing as a complete female in every respect, except that she does not mature or menstruate, and is somewhat small. In this instance, this individual was destined at conception to become a male, as shown by the male chromosomal pattern. Testicles were formed in embryonic life, but the stimulus to the testicles was removed, so that they atrophied. Then there appeared the *female* internal and external genitalia, which *forms in every agonadal individual,* as shown in experimental animals, the cause of which is entirely unknown. It seems there is some feminine stimulus present in all individuals before their sex is determined.

Thus, the gonad of the embryo may develop into a testicle, which may be perfectly normal and produce normal male external genitalia, but there may be degrees of cortical stimulation of that gonad at periods of its embryonic life so that varying forms of feminine changes occur in that embryo with the formation of partial or complete feminine internal and external genitalia. Certain adult and apparent males have enlarged breasts and male genitalia, including testicles (Kleinfelter's syndrome). Their testicles commonly show marked underdevelopment, sclerosis, and absence of spermatazoa. These men usually have a feminine chromosomal pattern, indicating that they were supposed to be females originally, but some stimulus must have caused this reversal of sex of the embryonic gonad, as has been produced in experimental animals. The stimulus was predominantly masculine and extended to the gonadal ducts, either directly or through the gonad, as evidenced by the atrophy of the Mullerian structures and development of the Wolffian ducts. Apparently the later removal of most of the masculinizing effect of these insufficient testicles has allowed some feminizing effects to progress, as they would in the agonadal individual, with the formation of well-developed breasts in these men. All variations up to a completely feminine genital tract in the presence of extremely reduced testes have been reported, these usually being in genetic males. The severe testicular impairment in early embryonic life allowed the feminizing effect of the neuter individual to dominate and form Mullerian duct and feminine urogenital sinus changes. All degrees of variations between true ovaries, testes, under-developed, or completely missing gonads, have been produced experimentally in animals regardless of their genetic sex.

The hormonal theory of stimulation of and stimulating effects of the cortex and medulla of the early gonad has caused great research in the study of experimental animals, by administering androgens or estrogens. It has been found that androgens do not alter the sex type of male embryos, but do masculinize female embryos. When the hormones are given before the female embryo has developed its somatic sexual differentiation, a marked change of masculinization is formed, with the production of a prostate and masculine external genitalia, but always the ovaries remain essentially normal except for their depressed state. These are effects after the ovaries have been formed, but before the mullerian or Wolffian duct structures and urogenital structures have been differentiated. On the other hand, experimental studies of the effects of estrogens on the male has shown no definite change, and this might mean that there is a protection from estrogenic hormones since the mother of the embryo and fetus contains normally such a large amount of circulating estrogen.

This experimental data, which has been summarized by Jost and added to so much by his own original researches, include the concept of an essentially feminine gonadless sex type in which the ovaries, if formed, may bring the genital tract to functional activity. If masculine factors impose masculinity, then they push back femininity. Thus abnormalities result from excess of masculinizing factors in the female, or deficiency of masculinizing factors in the male, allowing the female effects to come through in some parts of the genital tract. In rare instances, the masculinizing effect may come from the mother, as from a masculinizing tumor of the ovary, arrhenoblastoma, or a masculinizing tumor of the adrenal gland, or possibly adrenal hyperplasia, or, more recently, the administration of androgens to the mother. This includes some of the progestational compounds which have been used in pregnancy, and which are known experimentally to have some androgenic activity.

In summary, we have either normal male or normal female in both chromosomal, gonadal and body cells, with matching of first, the sex chromosome (of all the cells of the body), second, the testis or ovary, and, third, the external and internal genitalia, aside from the gonad. Secondly, we have gonadal dysgenesis (or gonadal agenesis), in which the gonad does not form to be either an ovary or a testicle, in which instance the individual, whether chromosomal male or female originally, will always develop female somatic changes, with tubes, uterus and vagina and female external genitalia. Or, we may have a gonadal dysgenesis in which an ovary or a testicle forms and then atrophies, in which the individual will have a female configuration, but may have a chromosomal male or female sex. Then, there may occur the *hermaphroditismus verus,* with a separate ovary and separate testicle, or an ovary and a testicle combined on one or both sides, or with perhaps a normal male or female gonad on the other side. All of this seems to be caused by stimulation, first of the gonad to become one type or another, then removal of the stimulation. More frequently, there occur the various forms of partial hermaphroditism, in which there are varying degrees of stimulation, of either the cortex (female) and medulla (male) of the gonad, so as to produce stimulation of either the mullerian ducts, completely or partially, or stimulation of the Wolffian ducts, completely or partially. Also, it is to be noted that androgens from the mother, whether they come from an arrhenoblastoma, the adrenal gland, as hyperplasia or tumor, or by hormones that have been administered as androgens or progestational compounds, may affect the embryo or fetus, depending on the age at which the hormone is present, and the apparent sensitivity to the hormone. Thus, varying degrees of masculinization may occur in an embryo or fetus, if androgens are given after the ovary itself is formed, but before the mullerian duct structures are completely fashioned. The urogenital sinus particularly may be affected by masculinizing hormones, changing the external genitalia in the case of the female. This is a form of hermaphroditism, and may not have an origin in the fetus itself. Enlargement of the clitoris and virilism developing in the child after delivery, particularly near puberty, may be considered a type of hermaphroditism, though it does not originate in the gonads, as it would seem to in the usual consideration of hermaphroditism.

TREATMENT

The treatment of these various changes is mainly directed toward the more obvious form of the sex of that individual, making certain surgical corrections, and perhaps some hormonal changes in that individual. First, gonadal dysgenesis is of considerable importance in gynecology, because it is not infrequently seen. These young women have not reached puberty, although sixteen, eighteen or twenty years of age, are somewhat short of stature, tend to have the web neck (the Turner syndrome), have under-developed breasts, under-developed external genitalia, although there may be present a subnormal degree of hair, and have the atrophic, thin, pre-pubertal type of vagina, and extremely small uteri and tubes. Buccal smears show the male type of chromosomal pattern, with presence of the chromatin mass in the nucleus in less than ten per cent of the cell's, and if one biopsies the minute linear strand of gonad, one finds very atrophic appearing stromal cells. This, though previously thought to represent ovarian tissue, apparently does represent an extremely under-developed testicle (medulla). Biopsy is not necessary, and the finding of the male chromosomal sex pattern is sufficient to begin continuous and cyclic treatment in these individuals. The treatment consists of the giving of estrogens, such as estrone sulfate 1.25 mg. (Premarin) daily for two or three months, which causes a definite growth of the breasts, the appearance of axillary and increased pubic hair, thickened vagina, and enlargement of the uterus. After two or three months time, the estrogen may be given cyclically, as twenty days out of each twenty-eight days. In order to precipitate a better withdrawal bleeding than estrogen alone will give, progesterone may be given intramuscularly in oil, 50 mg. on one or two successive or alternate days, as the estrogen is being terminated each cycle, three or four days after which a normal type of menstruation will appear. The more recent and newer, exceedingly potent oral progestins will be preferable to the use of injectible progesterone. Such substitution therapy probably should be continued until the usual age of the menopause, when it may be discontinued as with normal women, or very small doses of estrogen may be used as necessary for menopausal symptoms which are to be expected after the body has been tuned to these hormones over these many years.

The psychological effect of this treatment is remarkably satisfactory. The patients feel they are more female, more normal, and they are much pleased to see the growth of the breasts, hair and body fat. They tend to marry, have normal sex relations, with normal orgasm, and have all the feeling of a wife and mother. Their only difference is that they must adopt their children, and can never expect to become pregnant.

Of particular interest are the studies of Money, Hampson and Hampson (1955), from a psychiatric point of view. They found that the majority of these young women with gonadal dysgenesis are entirely feminine psychologically, although they are chromosomal males. From their studies, they concluded that the psychological sex is determined by genital sex and sex of rearing; that is, if they are considered to be females from infancy on, and are reared as females, then they have female interests; if individuals are reared as males, even though they are genetic females, they have male interests and male psychology. This is in contrast to our previous considerations in which we felt that maleness and femaleness were primarily inherent (Novak), and that it was most important to follow the psychology of that individual regardless of their genital findings, and that we must wait to see what psychology will develop in many instances, and to follow the trend as it developed. But this new and extraordinary approach gives an entirely different viewpoint in this matter.

In the treatment of other and more obvious forms of hermaphroditism, where there may be changes only in the external genitalia, or changes in the internal genitalia, or the presence of an ovary and testis, the newer approach is to follow the sex of rearing, in which there has developed a psychology of that sex, which apparently cannot be changed without severe and deep-seated psychogenic conflicts, except in certain individuals who may be homosexuals or be transvestites. As a rule, if hermaphroditism or opposite chromosomal sex is found after the age of infancy, the tendency is to follow the sex of rearing. If there are testicles present, along with a vagina and uterus, and the person feels that she is a female, the newer approach suggests that the testicles should be removed. In the very young infant with hypospadias and intra-abdominal testicles and absent vagina, uterus, tubes and ovaries, this approach tends toward removal of those testicles and later construction of an artificial vagina. This has developed because of these psychological investigations which seem to mean that any individual can become either male or female from the sexual point of view if started in extremely early life. The reason these individuals are made females instead of males is because a vagina can be fashioned between the rectum and bladder, whereas an erectile penis cannot be constructed, and the extremely hypospadic male cannot be made normal by present surgical procedures. This seems a rather drastic approach, and perhaps there will be a swing away from this contemporary idea. Various plastic procedures are used as indicated in other instances.

ADRENAL HYPERPLASIA, ADRENAL TUMORS, AND ARRHENOBLASTOMA

Virilism or masculinization from adrenal hyperplasia may occur in fetal life, in the presence of normal, though depressed, ovaries of the infant, and with lack of development of the Mullerian duct structures and urogenital sinus, and with stimulation of the Wolffian duct structures, and masculine urogenital sinus changes. More often these changes are in the urogenital sinus alone, and are more readily corrected. In these newborn infants, this degree of masculinization of a chromosomal and genetic female, which may or may not be recognized, is often associated with shock in the infant, due to electrolyte imbalance caused by the adrenal cortical hyperplasia, in which there is severe deficiency of sodium ion, and often an excess of potassium ion. Later, there may be weight loss, vomiting and dehydration. If the cause is recognized, it may be corrected by administration of fluids containing proper amounts of sodium ions, and the child may survive, to be treated thereafter by cortisone to depress the adrenal cortex. Surgical correction of the urogenital sinus abnormalities is usually satisfactory, and not complicated, consisting of incising the apparent hypospadias posteriorly, to reveal the normal female urethra and normal vagina. This is followed by excision of the enlarged (penile) clitoris.

The masculinizing adrenal hyperplasia is of congenital origin. It may not be recognized at birth, the slight changes of enlargement of the clitoris being the only obvious deformity. These children are said to grow more rapidly than normal up to the age of about ten years when the epiphyses close, and no further growth occurs. While this condition occurs

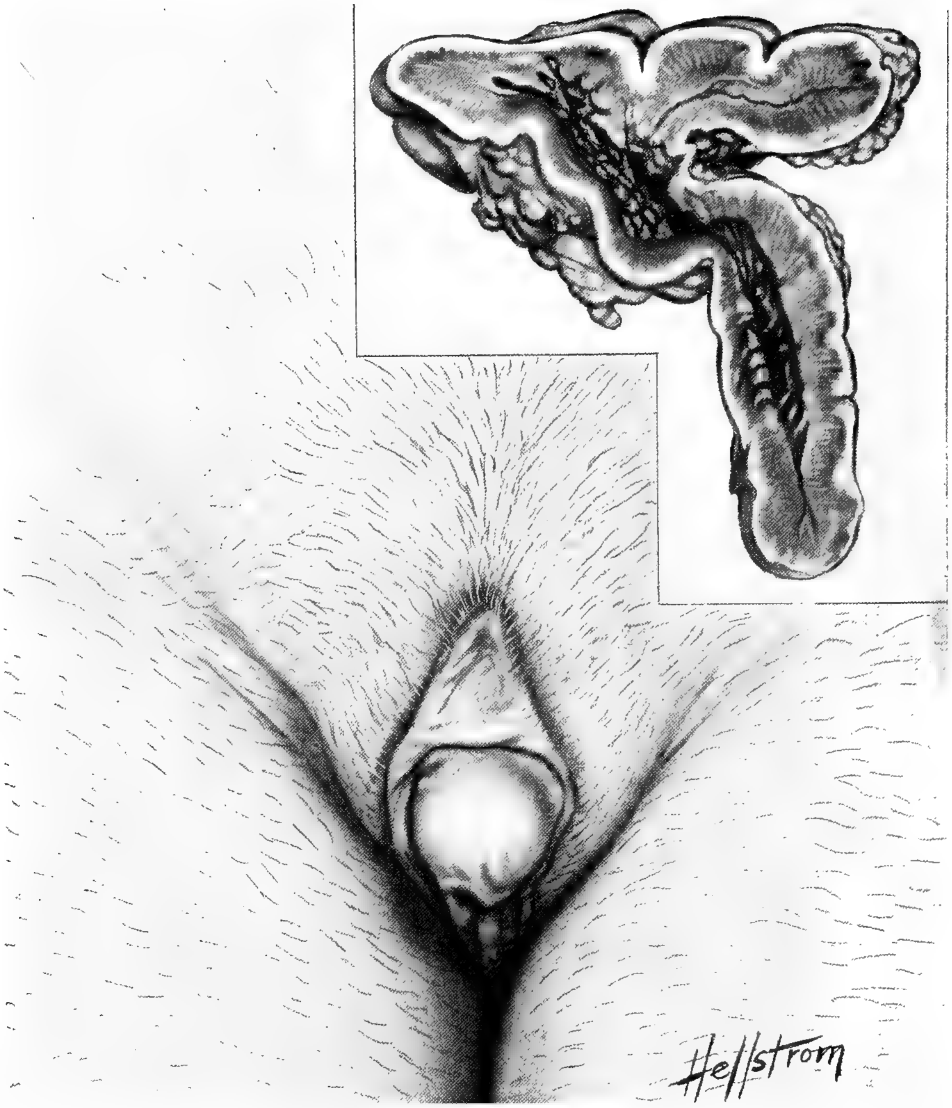

Fig. 309. Congenital adrenal hyperplasia, age 18 years. Primary amenorrhea, hirsutism, enlarged clitoris, rather short in stature, and muscular build. 17-keto-steroids, 120 mgm. per 24 hours. Peri-renal air injection suggested tumor. Excised adrenal shows hyperplasia.

more frequently in girls and is more obvious here, it also occurs in boys, producing macrogenitosomia praecox. The adrenal glands are greatly enlarged, mainly in the reticular zone of the cortex. Normally the reticular zone makes up one-third or one-fourth the width of the cortex, but in this condition it comprises up to ninety per cent of the width of the greatly thickened cortex.

More often the adreno-genital syndrome is recognized later in the life of the child, appearing at the age of ten or twelve and becoming more obvious at fifteen, sixteen or eighteen years. At this time, the child is obviously shorter than normal, has increased growth of hair on the face, body and legs, has a marked muscular development of the arms, legs, thorax and abdomen. The clitoris shows marked hypertrophy, the vagina and uterus are quite small, and if the ovaries are inspected they are found extremely small, almost cord-like in gross appearance, and would seem impossible of any further development. The 17-ketosteroids are remarkably elevated in the infant, perhaps to 20 mgm. excreted in twenty-four hours, whereas in the child at puberty these androgens may approximate 50 or 100 mgm. per twenty-four hours. Perirenal or presacral injections of carbon dioxide, oxygen, or air, although the latter is not to be preferred because of the danger of air embolism, may demonstrate in x-ray films marked enlargement of the adrenal glands. Cortisone, or its related compounds, are given intravenously, intramuscularly, or by mouth, although the parenteral injection seems to give a more prolonged effect with smaller dosages and may be used only twice weekly. Such treatment is followed within a few hours or days with a marked decrease in the 17-ketosteroid excretion. This acts as a diagnostic test in addition to therapy, as such a decrease does not occur if an adrenal tumor is present. It would appear that the special x-ray procedures and surgical exploration of the adrenal glands are not necessary at this time, if the therapeutic test with cortisone is used. Sufficient cortisone medication is given to depress the excretion of keto-steroids to three or four milligrams of 17-ketosteroids per twenty-four hours, and this is maintained indefinitely. A remarkable release of gonadotrophins follows, and the minute strands of ovarian tissue develop to normal size, produce estrogenic hormone, ovulate, and cause menstruation. These individuals may become pregnant and have normal children. If the 17-ketosteriod excretion does not decrease, then an adrenal tumor or arrhenoblastoma may be suspected. The even more rare Leydig cell tumors of the ovarian pedicle (hilar cell tumor) may be present.

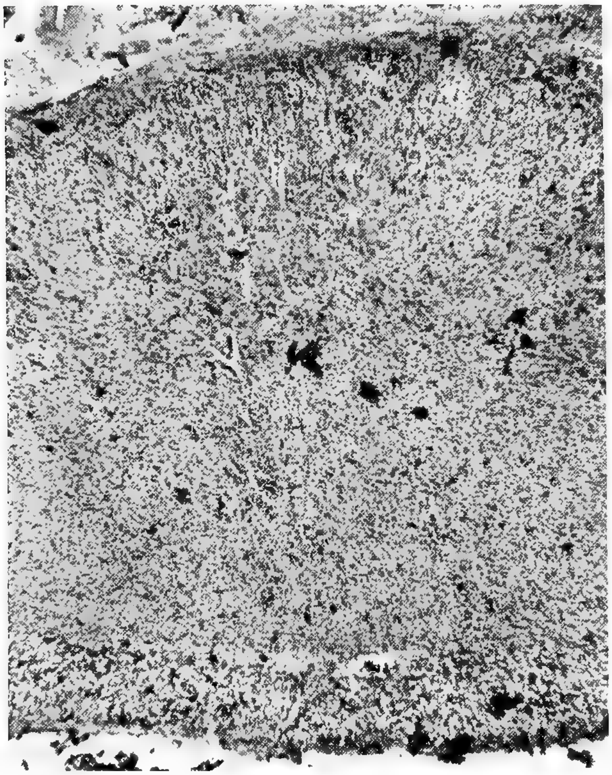
Fig. 310. Congenital adrenal hyperplasia. Note extreme hyperplasia of reticular zone. Formalin pigment is artefact.

Lesser degrees of adrenal hyperplasia may cause oligomenorrhea, or amenorrhea, with anovulation and sterility in the presence of only slight degrees of virilism. Elevated values of ketosteroids in the twenty-four hour urine specimens leads the way to treatment with the cortisone compounds, which may be followed by ovulation, normal menstruation, and pregnancy.

DISORDERS OF THE MULLERIAN DUCTS IN DEVELOPMENT AND FUSION, AND DISORDERS OF DEVELOPMENT OF THE UROGENITAL SINUS

On the one hand, a disorder of development of the Mullerian ducts on rare occasions is the complete absence of development of these ducts, so that there are no fallopian tubes, no uterus, and no cervix formed. The ovaries may be normal, or they may appear in abnormal development, as hypo-ovarianism, or one ovary may be absent, but this is not particularly related to the Mullerian ducts, having a different origin in the genital ridge itself. The complete absence of the fallopian tubes and uterus is seen on occasion,

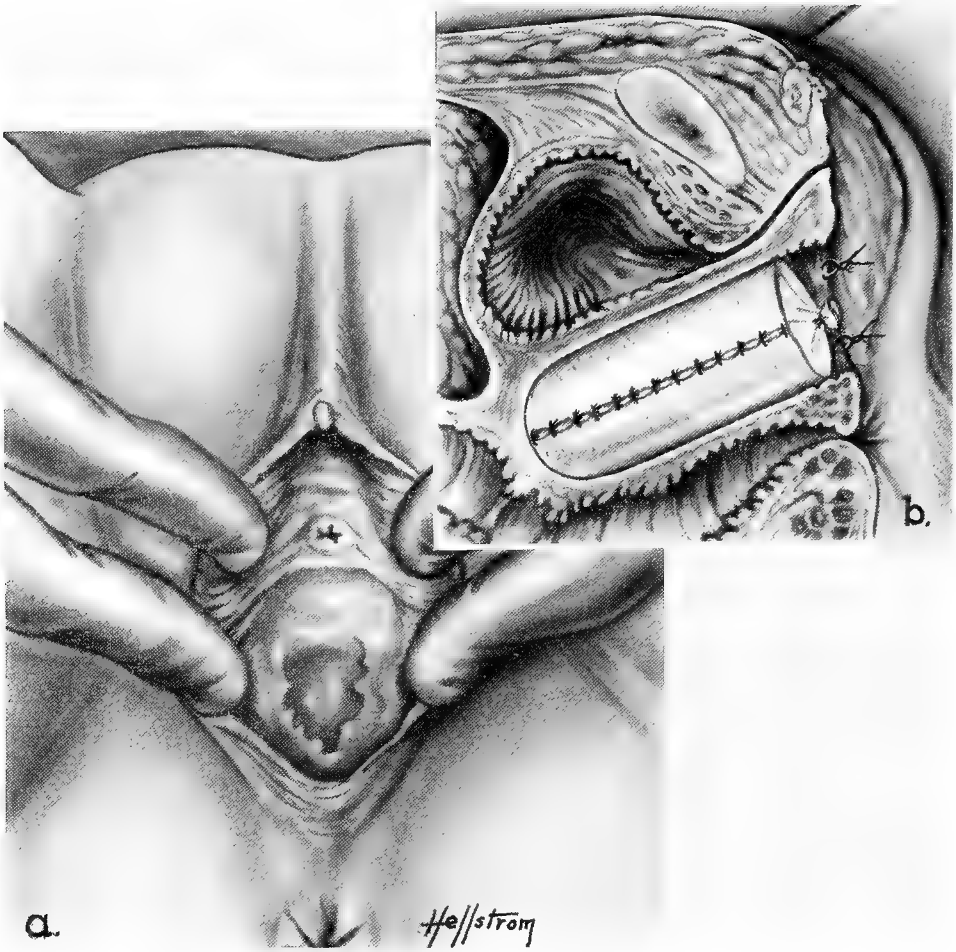

Fig. 311. Construction of vagina. Patient has absent vagina, uterus, tubes and ovaries. A foam-rubber prosthesis, encased in thin rubber, has a split-thickness skin graft sutured about it. This is placed in the dissected space for 10 days. The graft may take suprisingly well. (Counsellor operation).

and, of course, cannot be amenable to any treatment. In these patients, the external genitalia formed from the urogenital sinus may be perfectly normal, having had its stimulus from the feminizing effect of the early gonads. There may be present only a slight indentation of the vagina, or the vagina may extend in 3 or 4 cm., or on rare occasions the vagina may be of almost normal depth. These vaginas of varying depth usually otherwise appear normal, have rugae that are well formed, and, being covered with stratified squamous epithelium, respond to the estrogenic hormones, which are present as a rule in the adult in normal amount, although the uterus and tubes are absent.

Such marked abnormalities, namely, complete absence of any development of the mullerian ducts, often are associated with abnormalities of the urinary tract, in which there may be one kidney, or a pelvic kidney, or a fused horseshoe-type kidney. Always the urinary tract is to be investigated in these cases, particularly before any operative procedure is performed.

The next disorder might be said to be that of complete lack of fusion of the Mullerian ducts. In these not too uncommonly occurring instances, the fallopian tubes are normal, there being one on each side, and the uterus is divided into two halves, each containing a single lateral cornu and a rounded medial

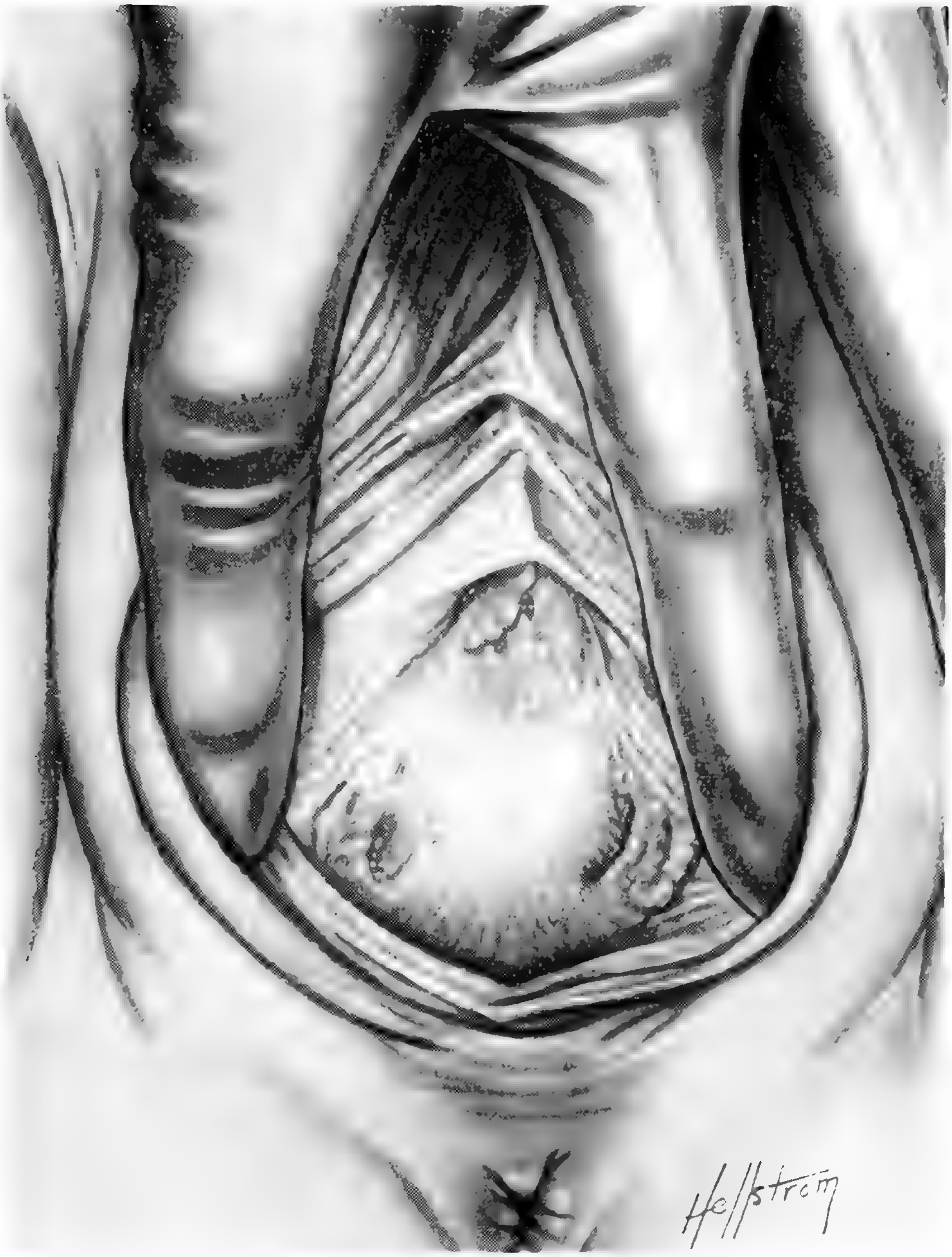

Fig. 312. Imperforate hymen with hematocolpos. The urethral meatus is obscured by the spread fold in the vestibule. The bulging thick hymen is opened by transverse incision evacuating the retained menstrual blood.

surface. In these instances, the halves of the uterus are as a rule smaller than a normal single uterus. In the region of the lower uterine segment medially, the bladder peritoneum extends between the halves of uteri and is attached to the rectum. A band of slightly thickened connective tissue is present beneath this peritoneum. It is divided with slight difficulty from the bladder and rectum during surgical procedures. Some have felt that this vesicorectal band, or septum, is a cause for incomplete fusion of the ducts. Vaginal examination in these instances of complete lack of fusion shows two separate small

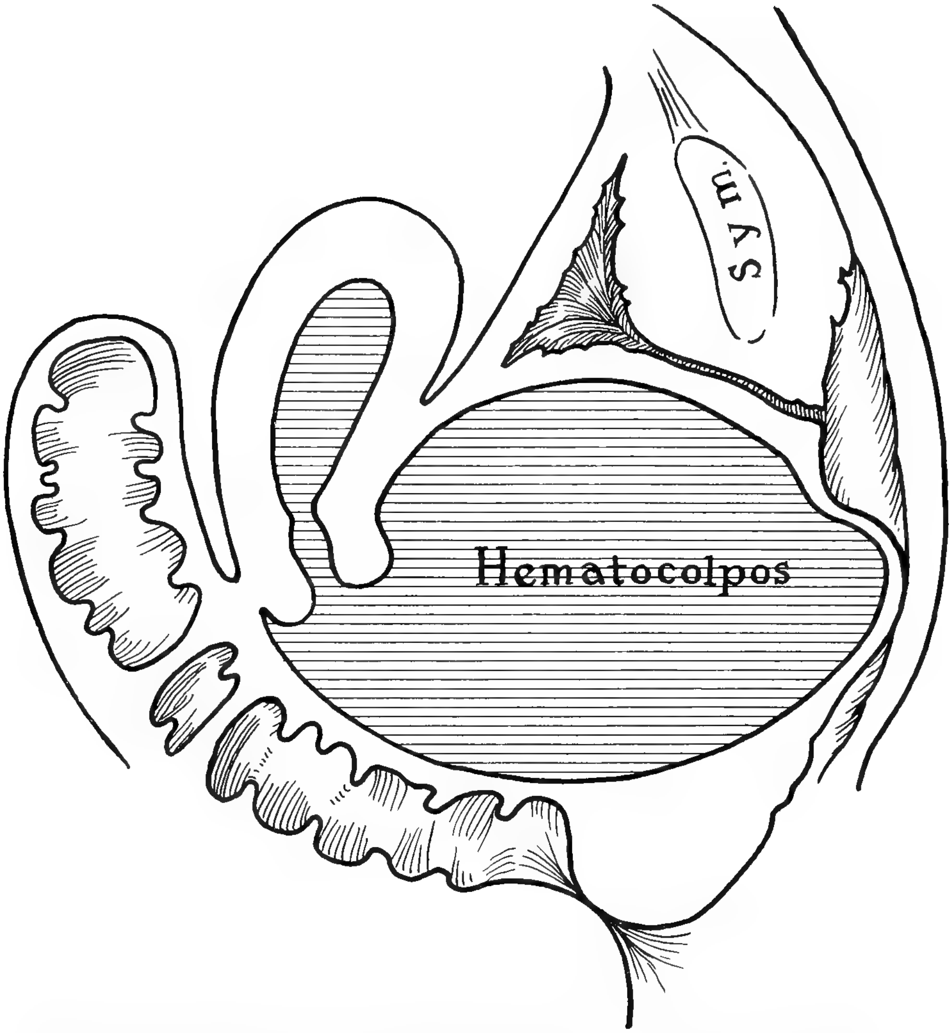

Fig. 313. Diagram shows vagina and uterus distended with menstrual blood

cervices, though closely approximated. As a rule, extending down between the two cervices there is a septum in the vagina, ordinarily extending all the way to the vaginal outlet, though sometimes the septum has been formed to only a partial degree. This would seem to indicate that the vagina is a part of the Mullerian ducts, although in the other instance with complete absence of the upper Mullerian duct structures, and in the presence of a vagina of normal depth, one would think that the whole vagina must arise from the urogenital sinus as an indentation. At any rate, the so-called double vagina instead of representing two separate vaginas is one vagina with a septum in the center. It occurs rather frequently and may be readily overlooked on pelvic examination.

Complete separation of the Mullerian ducts is known as uterus didelphys, and is the pure form of the lack of fusion of the ducts. In this form of lack of fusion, certain abnormalities in function are frequent. Rather commonly there is menometrorrhagia, though by no means do all of these uteri function in this manner. Not infrequently there is associated dysmenorrhea. Often sterility is a complaint, and repeated abortion is not uncommon in those who can become pregnant. Rupture of a half uterus may occur near term because the uterine muscle is not present in sufficient volume and arrangement to contain the term fetus. Especially when one-half of the uterus is under-developed, if pregnancy should occur in it, rupture in the early months may cause catastrophic findings of intra-abdominal hemorrhage and shock. Later complications in pregnancy include dystocia, an impossibility of delivering the baby because of enlargement of the other half of the uterus deep in the pelvis, which prevents passage of the fetus. After delivery, whether normally or by Caesarian section, postpartum hemorrhage is more frequent, and the uterus subsequently may develop late disturbances of function.

On the one hand, there are the obstetrical complications, and on the other hand the gynecologic complications. In addition to the functional difficulties of menorrhagia, dysmenorrhea, and sterility, there are the numer-

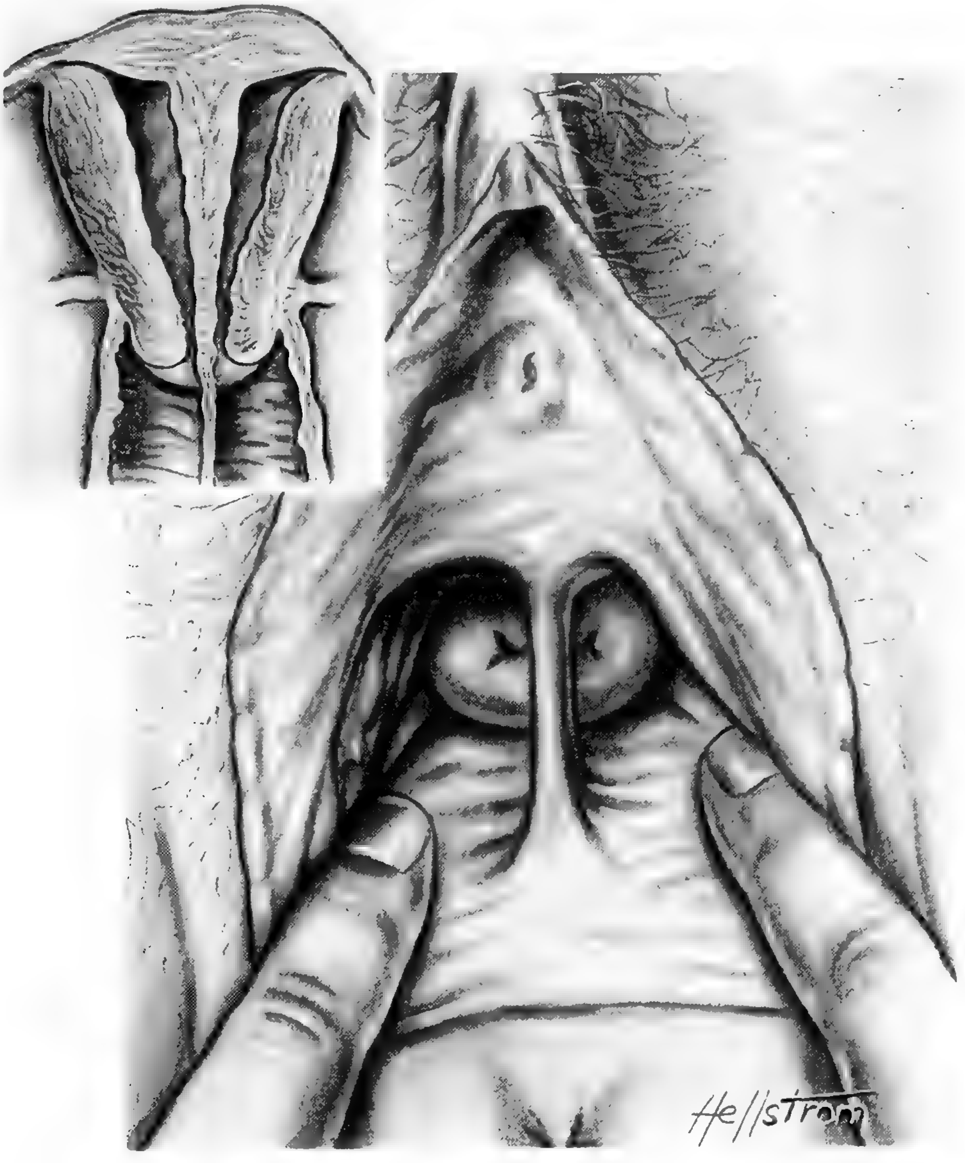

Fig. 314. Septate vagina, with septate uterus. Only a slight indentation is present in the fundus. The vaginal septum is readily excised, the rectum and bladder being carefully voided. The uterine septum may be excised through the cervix, but if there is doubt of the fusion of the two halves of the uterus, the uterine septum should be excised through an abdominal incision and hysterotomy.

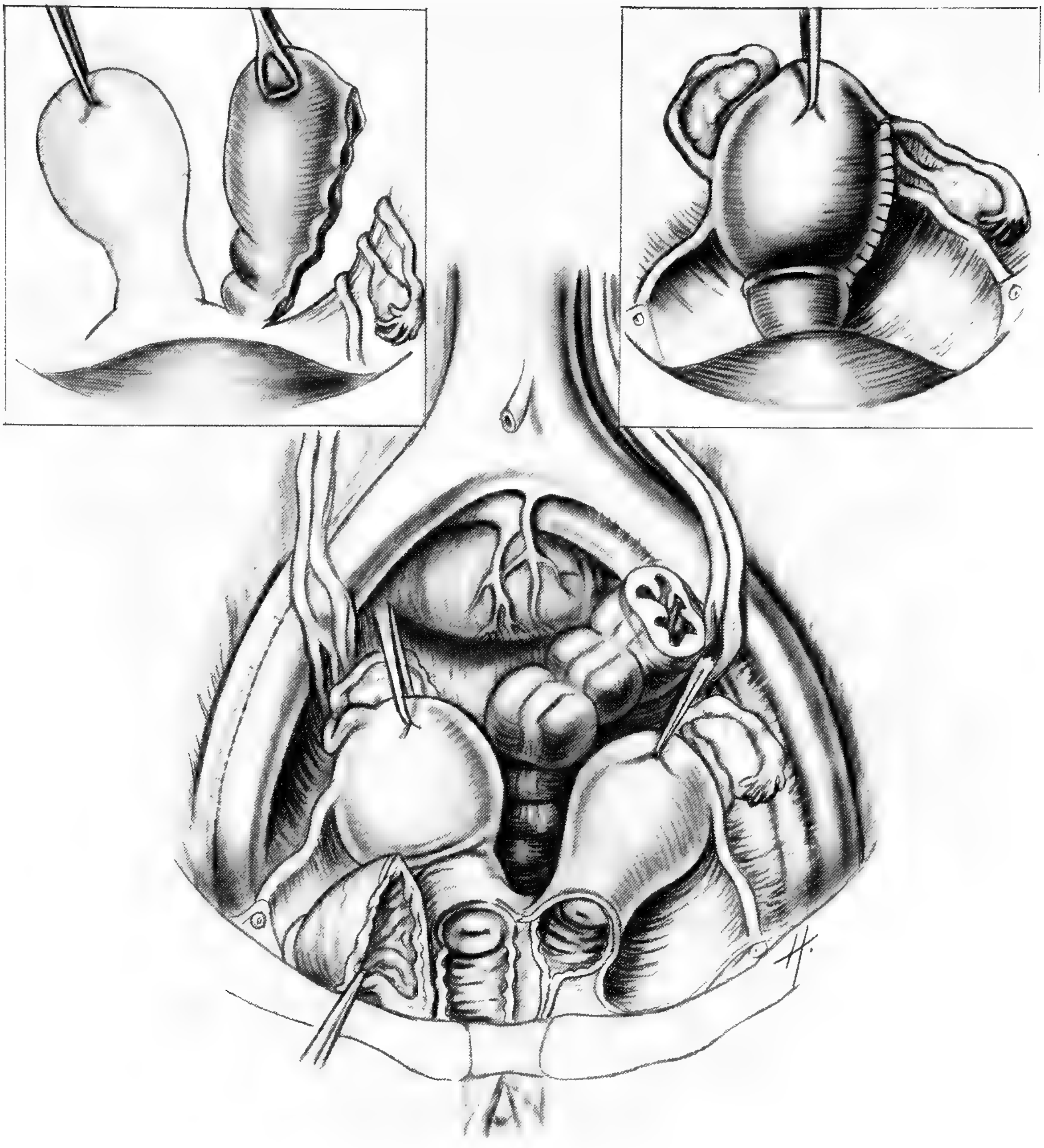

Fig. 315. Uterus didelphys, with rudimentary vagina on one side. Patient had two children. Because of pain in left side, intermenstrual bleeding and dysmenorrhea, and because of undetermined mass, exploration was performed. The left half of the uterus was excised, along with its vagina, and the large half was placed in the midline.

ous organic diseases that may affect one side more than the other. A rudimentary vagina on one side may be difficult to discover, may form a hematocolpos or pyocolpos extending into the broad ligament. Stricture of the cervix may occur on one or both sides followed by hematometrium or pyometrium. Myomas may involve only one side of the divided uterus. Lateral or retrodisplacement may be more marked with one-half the uterus. Unilateral adenocarcinoma of the endometrium has been described (Siegler). Endometriosis of one ovary and one side of the cul-de-sac seems particularly frequent, and seems associated with the tight cervical os that may possibly cause more retrograde menstruation on one side than the other. Unilateral salpingitis may occur: one may find acute gonorrheal cervicitis and salpingitis on one side with completely negative findings on the other, obviously indicating that the infected male entered the particular side. Congenital abnormalities always must be kept in mind, particularly when strange findings occur in the pelvis.

The diagnosis of uterus didelphys with its associated septate vagina may be extraordinarily simple, particularly when the septum in the vagina is well-formed in the midline and readily noted. This immediately arouses suspicion of the complete division of the Mullerian ducts. In the absence of the complete septum of the vagina, one may find small partial septa, or perhaps only bands that extend between the anterior and posterior walls at various locations along the vagina. These are rudiments of septa that were not complete. The finding of the double cervix, particularly one on each side of the septum, is always suggestive of complete lack of fusion, but such a double cervix may be present with a single uterus. The diagnosis of the lack of fusion of the uterus is made, of course, primarily by palpation, in which the halves of the uterus tend to fall far lateralward on each side. These lateral uteri may

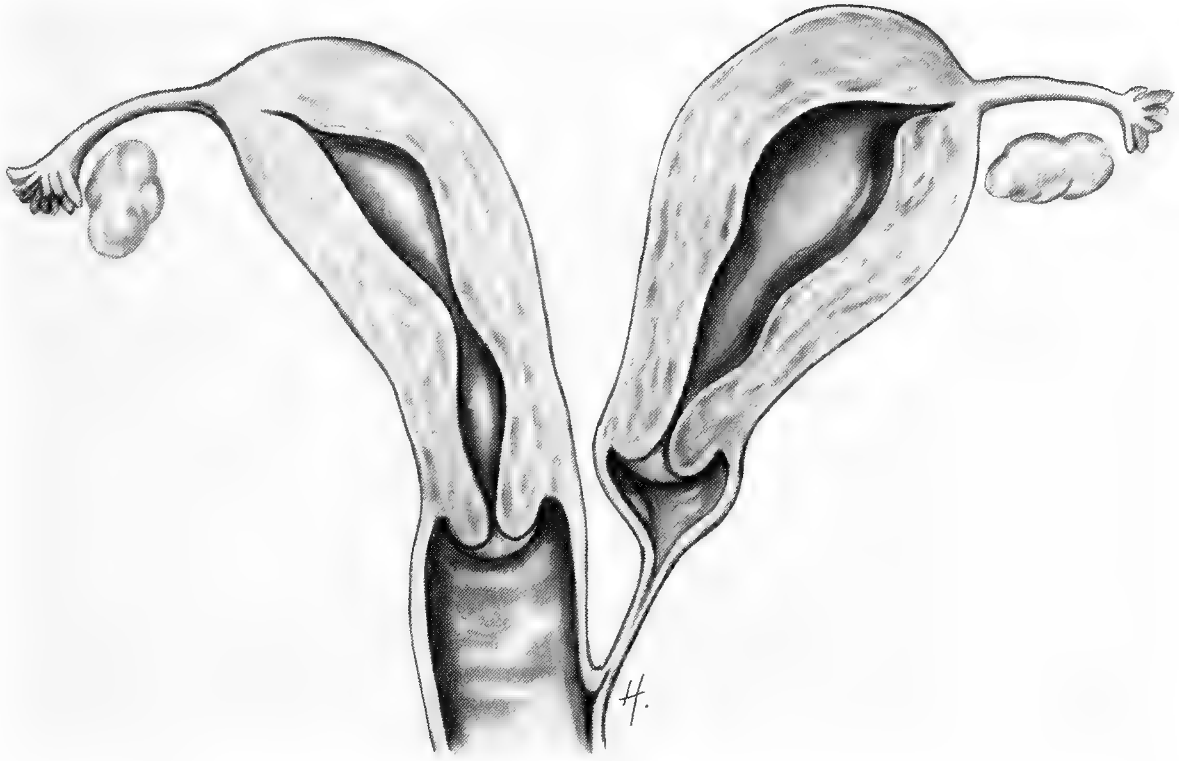

Fig. 316. Uterus didelphys with rudimentary vagina. Exploration for supposed ovarian tumor. The side with the small vagina was excised. Consideration should be given to joining the halves of the uterus and cervix together and grafting the small vagina into the larger.

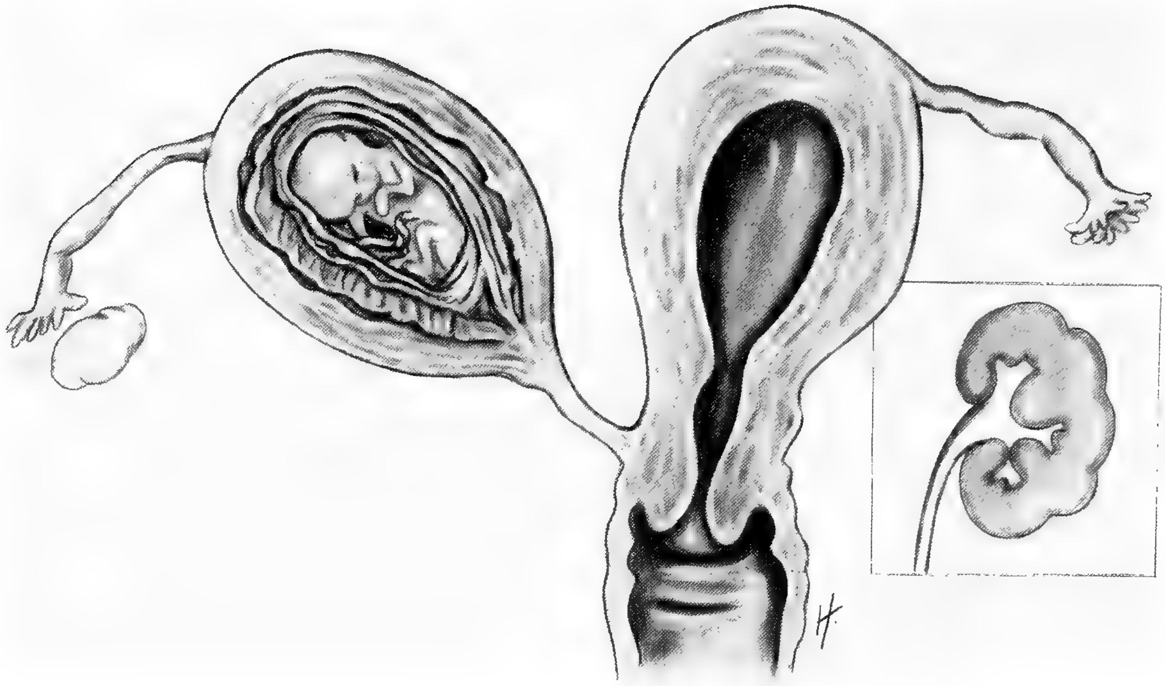

Fig. 317. Rudimentary horn with early uterine pregnancy. Patient was explored for ectopic pregnancy, after history of missed period, spotting, pain, and palpation of a velvety mass. Only one kidney was present. Patient moved to another part of the country. The family reported this pregnancy was delivered normally through the vagina!!

seem small or difficult to move into the midline with the palpating fingers. When one side is rudimentary as compared to the other, the diagnosis by palpation may be extraordinarily difficult, and especially when the smaller vagina is placed far lateral-ward in the broad ligament and not recognized. A pelvic examination may completely miss the medial separations, and this occurs when one enters one vagina only, feels a single cervix, and the uterus deviated to the side, with an apparent small mass far lateral on the other side. On a later occasion one may find a complete septum, with a lumen of practically normal size on each side. Occasionally, patients have had children, and the obstetrician has never discovered the opposite channel. The diagnosis may be confirmed by hysterosalpingography, which requires the use of a small cannula in each cervix, and each to be injected with the water soluble radiopaque medium to demonstrate the uterine cavities. In occasional instance, while there may seem to be complete lack of fusion, an opening may be found above the two cervices joining the upper cervical canal.

The treatment of uterus didelphys is, in the first place, no treatment, unless there are marked symptoms or associated pathological findings, or a history of sterility or repeated abortions. Surgical approach is not indicated unless there are reasons for the surgery. In patients with severe dysmenorrhea, the cervices may be dilated at intervals because they do tend to have a congenital stricture. If there is pelvic disease readily palpable, associated with symptoms, as endometriosis with pelvic pain and dysmenorrhea, chronic inflammatory disease with disabling symptoms, or myomas with pelvic pain and menorrhagia, then operation may be indicated. In such an instance, conservative excision of the endometriosis, or inflammatory disease, or myomas is performed if possible. Not infrequently a unilateral or hemihysterectomy may be necessary, because of the adnexal and uterine disease confined to this side. In these instances, one draws the remaining half of the uterus up into the midline, fashions a new broad ligament from the opposite side to maintain it in position, and attaches the round ligament from the excised half to the medial portion of the remaining uterus. This remains in the true sense a half uterus, and it may or may not be useful for reproduction. Many of these uteri do not carry a pregnancy to term, and there may be complications. However, pregnancy is encouraged and complications are met as they are encountered.

In about 1900, Strassmann of Vienna, devised various operative procedures for the separated uterus. First, he removed some of the septum from below through the vagina by crushing and cutting; in others, he delivered the two corpora of the uterus into the vagina through a colpotomy incision, incised and sutured the halves together, and then replaced the uterus in the abdominal cavity. In others, he made an abdominal incision, incised the halves of the uteri medially and

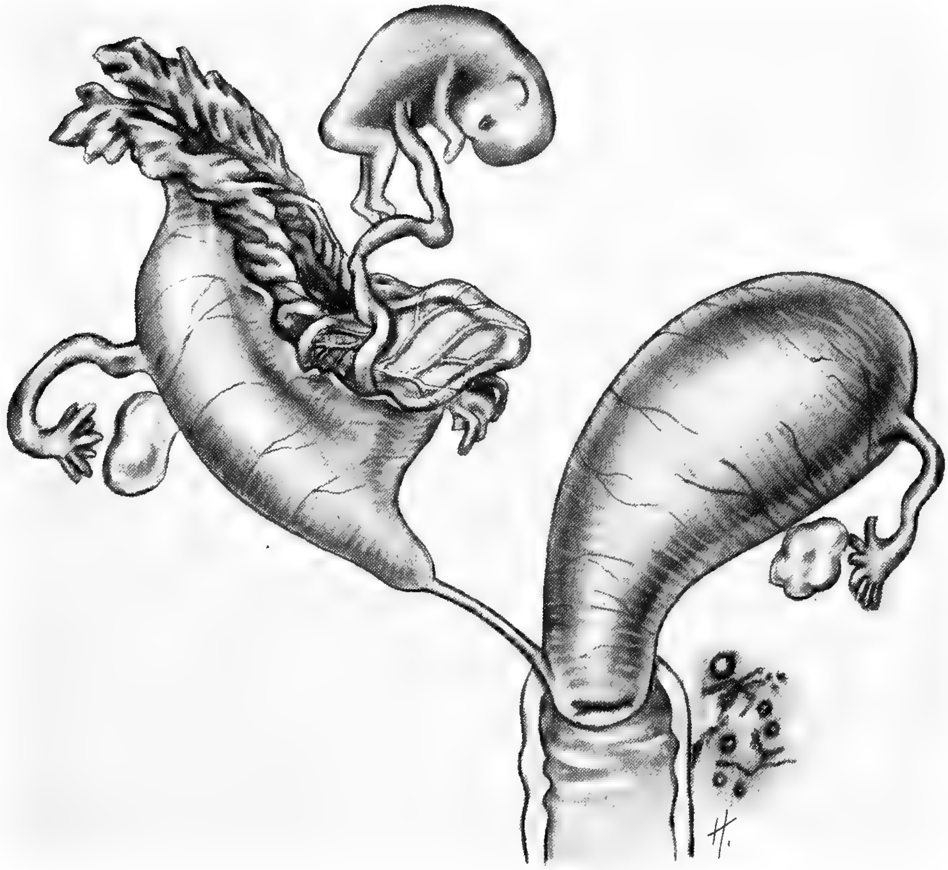

Fig. 318. Rudimentary horn of uterus, containing pregnancy, which ruptured at ten weeks. Severe hemorrhage ensued. This rudimentary portion was excised. It is strange that the sperm could travel up this very small canal. Endometrial implants are present in the opposite side of the cul-de-sac. Subsequent normal pregnancy and delivery.

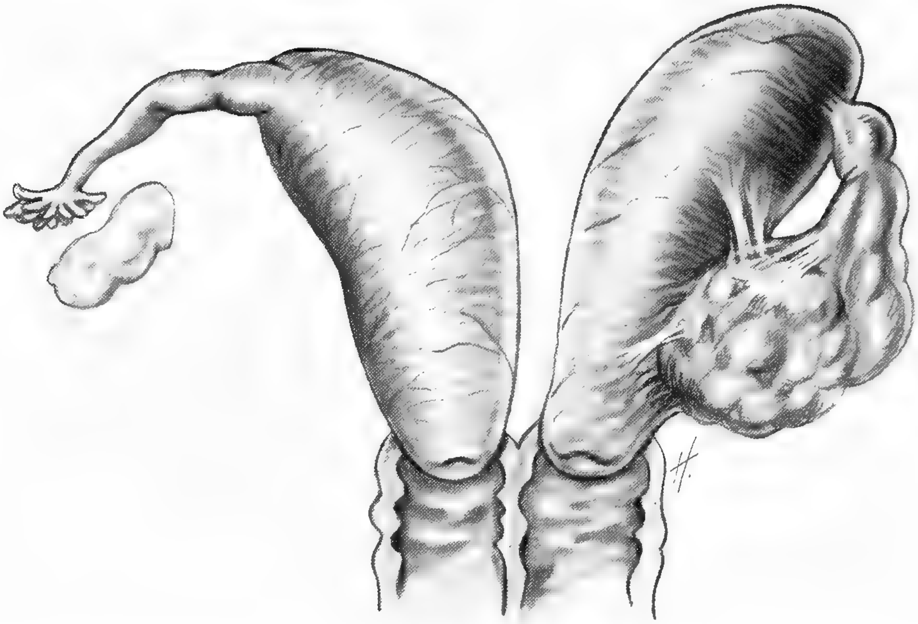

Fig. 319. Uterus didelphys; completely separate halves of the uterus and vagina. Subacute salpingitis with pyosalpinx and tubo-ovarian abscess. Gonococci were cultured from the tube and its associated cervix, whereas cultures from opposite tube and cervix were negative. Pre-operative diagnosis was probable tubal pregnancy. Postoperative treatment with penicillin.

sutured them together. These cases were followed by good results, with pregnancies in a majority. This all but forgotten operation has been revived by the son of the originator, now in Houston, and it is being accepted with much interest recently. The fear that the approximation of such halves of the uterus might not hold and be followed by rupture during pregnancy has not been borne out by the relatively small number of cases that have been reported. This operation is to be performed only with the history of repeated abortions, as this is the primary indication. Since half of a uterus may carry a pregnancy to term, always it is given this chance, and preferably more than once, before major operative procedures are performed. The uterus with complete septum may be improved for normal function by removal of the septum, particularly if there is sterility or repeated abortions.

While the uterus didelphys, with its complete reduplication, is the pure form of lack of fusion of the Mullerian ducts, varying degrees of separation of the Mullerian ducts may occur. There may be a double cervix and practically separate uterus but fused together in the midline with a deep groove at the top. There may be a complete septum through the uterus down to the cervical os. Such septa may be excised through the vaginal approach, in order to afford more room in the uterus for pregnancy, particularly if abortions and abnormal bleeding have occurred. There may be a double cervix and single uterus without septum. There may be a single cervix and completely, widely separated corpora of the uterus, or rather a half corpus of the uterus. Varying degrees of indentation in the fundus of the uterus may indicate the slightest amount of lack of fusion. This may be known

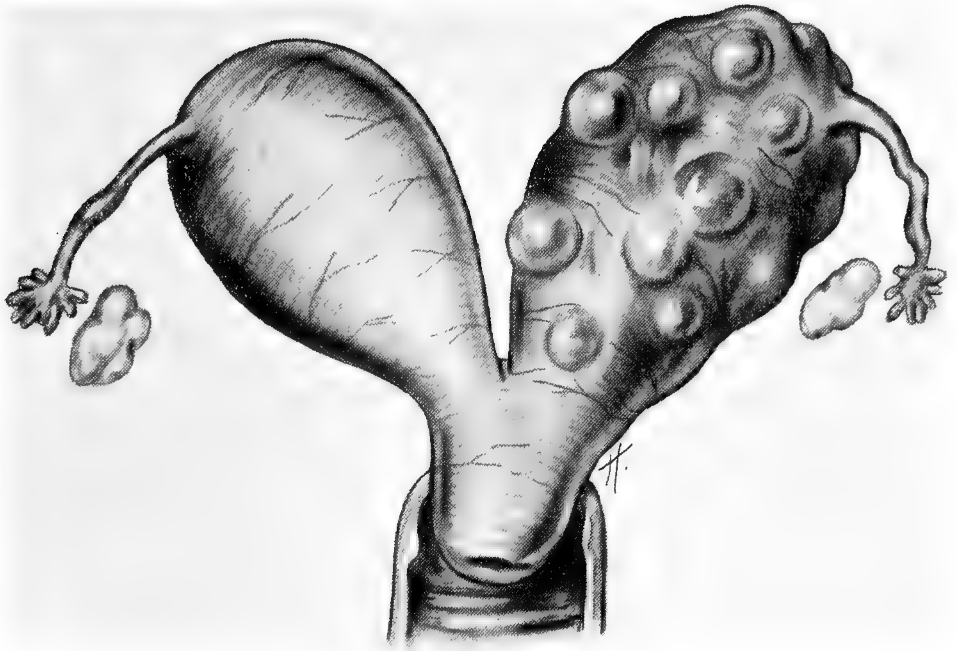

Fig. 320. Bicornuate uterus (uterus bicornis, unicollis), with multiple myomas on one side. Menorrhagia develops frequently, with or without myomas. In older women, hysterectomy may be necessary.

as an arcuate uterus, the arc dipping down between the cornua.

These varying abnormalities, of which some represent a rather marked lack of fusion, and others a very slight lack of fusion, may or may not be associated with symptoms. Gynecologic symptoms include dysmenorrhea, menorrhagia, and sterility, and obstetrical symptoms involve recurrent abortion, dystocia, postpartum bleeding, and those related to subinvolution of the uterus.

The diagnosis of these forms of lack of fusion may be obvious, if a divided corpus is felt extending widely to each side of the cervix, but it is not so readily suspected when there is a single cervix, or an essentially normal uterus with a septum. The latter may be discovered only if hysterosalpingography seems necessary for other reasons, as sterility, or after curettage for functional bleeding, when the septum or separate cavities may be found. Sometimes these septa extend throughout the length of the uterine cavity, but more frequently a small and incomplete septum may be felt in the very fundus of the uterus. The more obvious septa may be excised after the cervix is widely dilated, and if necessary the uterus may be packed. On occasion the septa may be excised by an abdominal incision, after transverse incision into the corpus of the uterus. With this approach, the septum can be more carefully removed and bleeding areas more accurately ligated, after which the corpus of the uterus is re-approximated by layers of sutures.

Again, two points are to be emphasized with reduplications of the genital tract. In addition to the difficulties of diagnosis that may occur, and the necessity for a suspicion of congenital anomalies when peculiar situa-

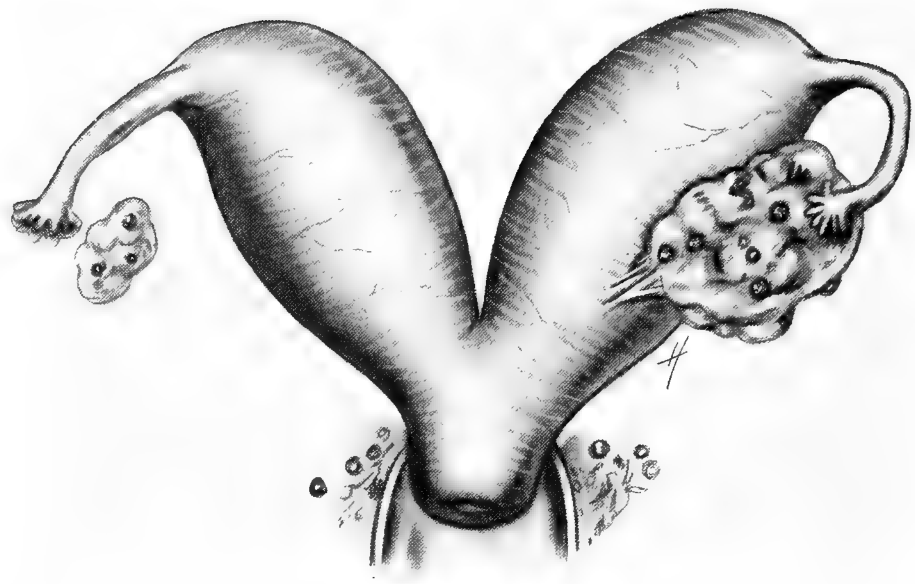

Fig. 321. Bicornuate uterus. Many implants of endometriosis are present in one ovary, a few in the other, and rather marked implants in both sides of the pelvis.

tions are present, it is to be remembered that other congenital anomalies may be associated, particularly those of the urinary tract. One kidney may be absent; there may be a single pelvic kidney down under the pelvic brim or there may be a horseshoe kidney, both kidneys fusing in the midline. The ureters may be abnormally placed or reduplicated. Other congenital anomalies in the body may be associated with anomalies of the genital tract. The other real point is that the treatment of these anomalies ordinarily depends upon the presence of symptoms, including abortion and sterility.

In the treatment of the septate vagina, as a rule the septum is excised, a rather simple procedure, followed by approximating the mucosa along the line of excision. If the vagina is quite functional, and the septum causes no discomforts, excision may not be necessary. Bands along the vagina generally are excised because they do impede sexual relations.

In the treatment of congenital absence of the vagina, or the deepening of the slightly formed vagina, one may use the Frank method of pressing a test tube or glass rod into this area with constant effort, many times daily over many months. Apparently this may produce a small vagina this way. However, this method does not seem too satisfactory.

The Baldwin operation consists of drawing an isolated loop of terminal ileum between the bladder and rectum, opening it into the perineum, and then crushing the spur between the loop. It is said to form a well functioning vagina, and there are instances in which the columnar epithelium of this ileum is said to have disappeared and been replaced by squamous epithelium. However, this operation is rarely performed, because of the risk of intestinal resection and anastamosis. Wharton suggested the dissection of the area between the vagina and rectum to its full depth, and the introduction of a balsa wood prosthesis covered with thin rubber, which had been sterilized, to be left in place for a long period of time, being changed at intervals. The squamous epithelium of the vestibule slowly extends up under this raw area, and completely epithelializes the vagina. This is a slow process, and the upper vagina heals imperfectly.

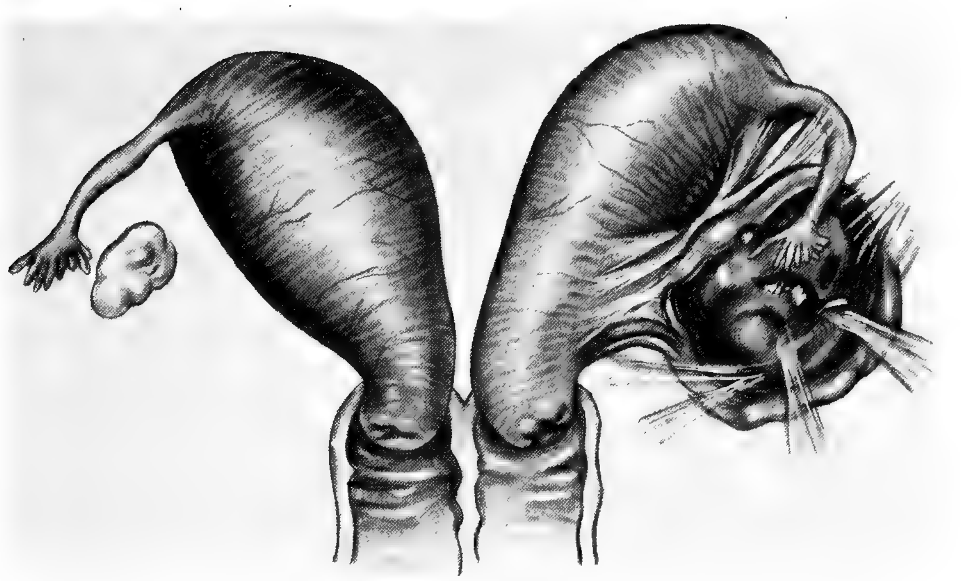

Fig. 322. Uterus didelphys. The uterus is in two complete halves, and the vagina is septate. An endometrial cyst has largely destroyed one ovary.

Various methods of placing skin flaps into a dissected area between the bladder and rectum have been used. Flaps have been moved in from the inner sides of the thigh, or from the labia. The Counsellor method seems the better one at the present time. A split thickness of skin cut from the inner surfaces of the thigh is attached with fine chromic suture around a sponge rubber prosthesis, covered with thin rubber. This prepared graft is placed in the freshly dissected area between the vagina and rectum, extending up to the peritoneum. All bleeding points must be controlled. The use of this sponge rubber is thought to cause much less necrosis of the graft, and to aid its attachment. The labia are sutured together over this prosthesis. After ten or twelve days, the sutures are released and the sponge rubber gently removed. Following this, there is introduced a very light weight, hollow, plastic prosthesis, which fits the form of the vagina, and is worn for a period of weeks or months. Often the healing is primary and essentially complete. Occasionally, broad areas are not epithelialized, and very prolonged care may be necessary before the epithelialization is complete. Sometimes, it may never be complete.

Congenital abnormalities of the urogenital sinus include absence of the lower vagina, which has been mentioned in the findings and treatment of the congenital absence of the vagina. Varying abnormalities in the labia majora or minora, or prepuce and clitoris, may be found on rare occasion. There have been reported in the literature a very few cases of double vulva, apparently a real reduplication of the urogenital sinus. The intact hymen is an extremely mild example of congenital anomaly of the urogenital sinus. The cause is unknown. In the pre-pubertal child it is of no importance, particularly if a small uterus is palpable through the rectum. Usually the imperforate hymen is first noted when monthly menstrual pains occur without external blood flow. The vagina gradually becomes distended with blood (hematocolpos), perhaps pressing the uterus far up into the abdomen. The uterus may be secondarily distended with blood (hematometrium), and even the tubes may show some distention (hematosalpinx). As soon as the

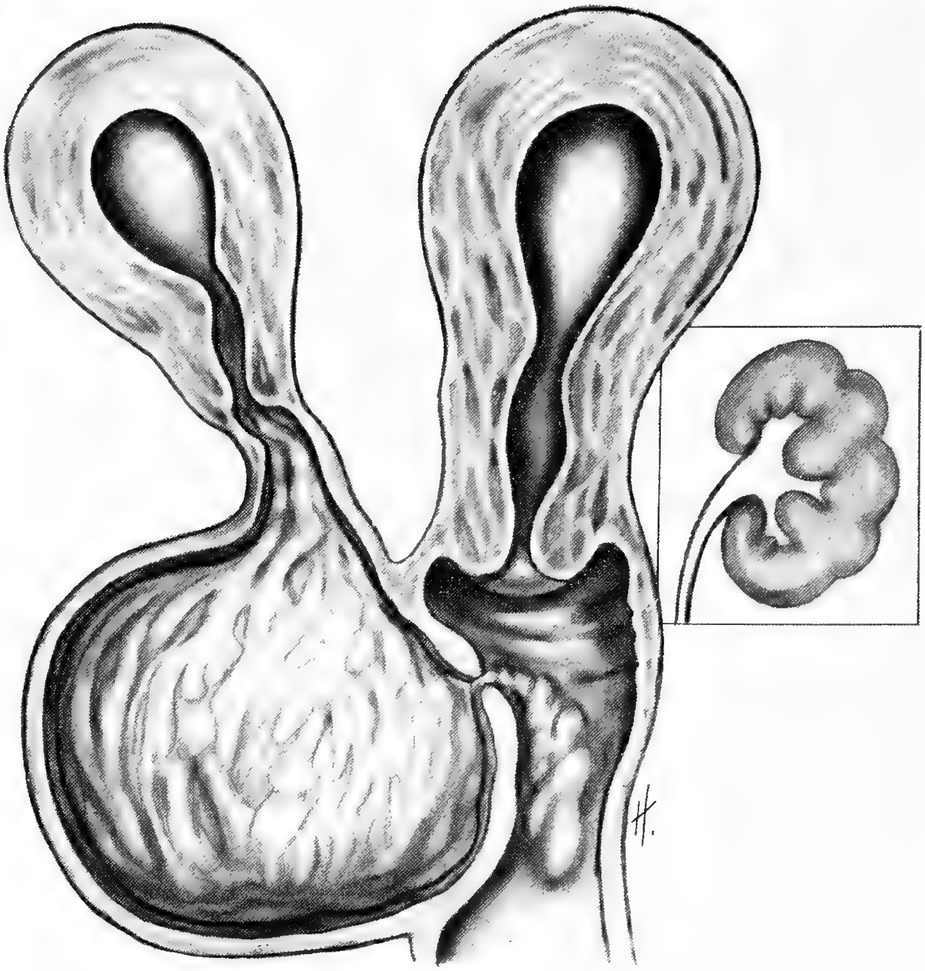

Fig. 323. Uterus didelphys with smaller half on one side, with obstructed rudimentary vagina and pyocolpos. Only one kidney was present. A window for drainage relieved symptoms of pain, fever and purulent discharge.

hematocolpos is recognized the vagina is incised transversely under anesthesia, allowing the free flow of the old chocolate blood. No drain is necessary, and cure should be permanent.

The more frequent abnormalities that are seen are those related to hermaphroditism in minor degrees. It is to be remembered that the external genitalia are more sensitive to the original stimulus from the early gonad, whether by a hormone or other method, and the nature of the stimulation is not yet understood. Evidently there is a control in which the external genitalia may tend toward the female or the male form. If a temporary masculinizing stimulus occurred in the early life in the embryo, male-like external genitalia may occur with normal female internal genitalia; often there may be formed the markedly enlarged clitoris, with closure over the vagina, so that the female urethra and vagina open together to the outside just beneath the enlarged clitoris, or phallus, as though there were a true hypospadias.

These changes at birth may be caused by a congenital adrenal hyperplasia with masculinization. As mentioned previously, these infants particularly may have electrolyte imbalance, and may succumb unless the condition is quickly recognized and rectified by the administration of sodium ion in particular, later to be treated with cortisone to depress the adrenal cortex. In these instances, first the chromosomal sex is determined by studying the buccal smear or blood smear. Secondly, cystoscopy is performed. If this is a masculinization of the urogenital sinus alone, the cystoscope readily enters the vagina beneath the female urethra. A posterior incision later is made through the false urinary meatus and the edges of the vestibule are sutured laterally. Readily there is formed a normal opening to the vagina. The enlarged clitoris, which is usually present, is then excised down to the base. While some effort has been made at intervals to save the tip end of the glands of the clitoris, because of its sensitive nerve supply, and resuture it after the shaft has been excised, this has largely been abandoned because of the difficulty in healing, and the apparent lack of necessity for such a procedure. The nature of the internal genital sex may be determined by exploratory operation in certain cases to determine if a uterus, tubes and ovaries, are present, after which the nature of the external abnormality becomes more obvious.

Recently, it has been determined that masculinizing changes of the external genitalia of the female fetus may be caused in utero by the administration of even mild doses of androgens, such as testosterone, or methyl testosterone, early in pregnancy. If the masculinizing hormones are given, particularly near the sixth week of pregnancy, these abnormalities may be found, not in all cases of female infants but in some of them. They are

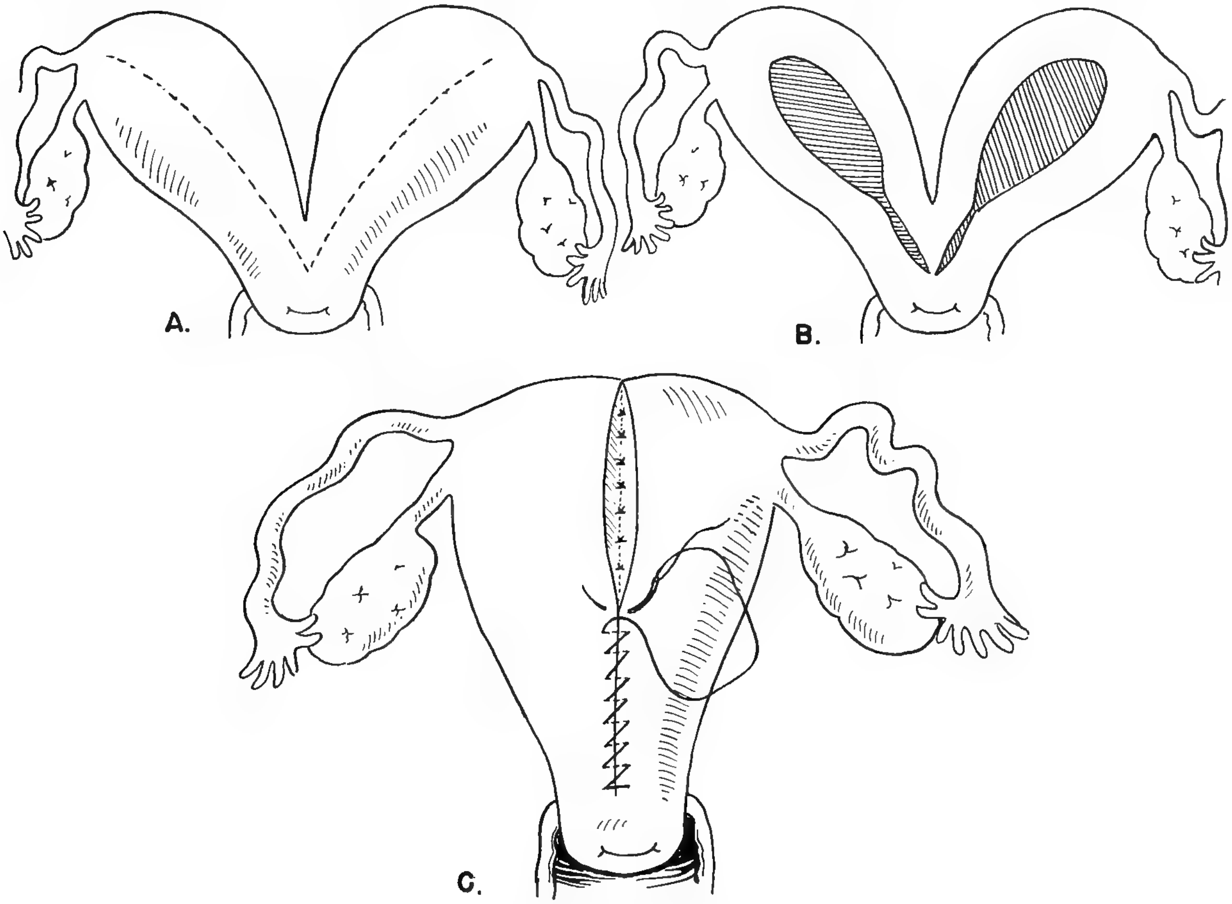

Fig. 324. Uterus bicornis, unicollis. The two halves of the corpus of the uterus may be joined together (the Strassmann operation), which is useful in cases associated with sterility and recurrent abortion.

treated in a surgical manner similar to those that occur with congenital hyperplasia of the cortex of the adrenal gland, or those that are true forms of hermaphrodites, with changes caused by the stimulus of the original gonad when it was in a masculinizing phase. The use of progestational compounds for the purpose of treating threatened abortion in early pregnancy may cause similar abnormalities. Oral preparations, as ethisterone (Pranone), particularly have been incriminated in this masculinization. It is remarkable that pseudohermaphroditism may be caused by the androgenic action of progestational compounds (and the latter are closely related chemically to the testosterones), acting as a hormone effect at a very sensitive time in early embryologic life.

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CHAPTER XIV

Sterility

It is estimated that ten to fifteen per cent of all married couples are unable to produce a child. While some of these couples are unconcerned about their inability to procreate, probably half of them consult their physician. Of those who approach the physician, about one-third do not pursue the study or investigation. On the other hand, the remaining two-thirds who seek help are most intense and highly concerned regarding their sterility and do follow, with great interest and cooperation, the investigation and treatment.

The term sterility is often qualified as relative sterility or absolute sterility. Relative sterility means that there may be some deficiency found in either the wife or the husband, or perhaps no abnormalities found in either to explain the cause of the sterility. Absolute sterility means that either the wife or the husband has a definite reason to explain his or her inability to procreate. Examples are the congenital absence of the uterus or the complete absence of any spermatazoa in the semen. Sterility is also spoken of as primary sterility and secondary sterility. The former means that the couple has not had their first pregnancy, whereas secondary sterility means that one or more pregnancies have occurred, but that subsequent pregnancy has not followed at the desire of the couple.

Some physicians have preferred the term infertility, feeling that there is less stigma or less discouragement in this term in contrast to sterility, which connotes an unhappy and a rather conclusive state, which leaves the patient discouraged at the outset. The word infertility seems more hopeful and less conclusive. Some have used the term infertility to indicate that the wife may become pregnant but is unable to carry the pregnancy to term, having spontaneous abortion or miscarriage on one or repeated occasions.

In any study it is obvious that both the female and the male are equally important. Investigation of the female requires consideration of three factors which cause sterility, namely organic disease, endocrine abnormalities, and psychogenic factors.

ORGANIC ABNORMALITIES

Of the organic abnormalities or diseases, congenital abnormalities may represent an obvious or occult cause of sterility. In women who may never have menstruated outwardly, there may occur the imperforate hymen, perhaps with accumulation of blood behind it, representing the hematocolpos; or congenital absence of the vagina, perhaps with a uterus that may menstruate and become distended with old blood; or there may be no uterus present at all. There may occur a normal vagina with absent uterus. With absence of the uterus, sterility is clearly absolute. But if a uterus is present with absent vagina, sometimes a connection can be made with the exterior and pregnancy may be possible. This has proved a most unusual situation. Congenital absence of the tubes has occurred, and the gonads may be absent, completely underdeveloped or of the opposite sex.

Varying degrees of lack of fusions of the Mullerian ducts may be definite causes of sterility. The deeply bicornuate uterus with widely separated halves with a single cervix is much less prone to become pregnant than is the uterus of normal size and conformation. The uterus didelphys, with completely separated halves of the uterus with separate cervices, and usually with septate vagina, is particularly a cause for sterility, recurrent abortion and difficulties with labor and puerperium, though not invariably so. Surgery in these degrees of lack of fusion is not indicated unless there is proven sterility or recurrent abortion. For a long time excision of one half of the uterus was practised. Of late, the Strassmann operation has received much impetus, in which the two halves of the uterus are joined together. While many had feared that such a uterus joined together would rupture under the stress of pregnancy, evidently good results are the rule.

Inflammations of the vagina and cervix might seem of little importance in causing sterility, because the majority of women with vaginitis and cervicitis readily become pregnant. Were this not true, one would suspect that the abnormal vaginal secretions, with changes in the normal alkaline pH of the cervix, and the toxic effects of bacteria and trichomonas and fungi, should have deleterious effects on the spermatazoa. One does treat such a vaginitis or cervicitis in any patient, whether sterility is a complaint or not. Some patients with infertility become pregnant soon after treatment of these infections alone, and there seems to be a causal relation in a small percentage of cases.

When spermatazoa are observed in the cervical secretions one hour following sexual intercourse (the Sims-Huehner test) one expects to find fifteen or twenty motile sperm per high power field. If immotile and fewer in number (and the analysis of the semen was found normal), one assumes that the secretions are inimical to the spermatazoa. More care is extended to the observation and treatment of cervicitis in these instances. If cauterization or conization are not performed, the cervix may be dilated to provide better drainage. Cultures of the cervical secretions may reveal pathogenic organisms sensitive to certain antibiotics. Appropriate therapy may be followed by improvement in the number and motility of the spermatazoa.

Cervical stricture undoubtedly may follow cauterization or conization of the cervix, and subsequent dilatations may be required. In many young women the cervices have congenitally small canals, which may be a factor in some cases of inability to become pregnant. Dilatation of these cervices may be of value, though not frequently followed by the desired result.

Acute anteflexion of the uterus on the cervix, which means a sharp angle anteriorly at the internal os, may be a factor in sterility. Some degree of anteflexion is present in thirty per cent of young women before pregnancy occurs, but in only a small per cent does this seem important in the inability to achieve pregnancy. In such instances the cervix may be dilated and a stem pessary, made of plastic material, may be sutured into the cervix and left in position for six weeks, after which the suture is divided and the pessary removed. In occasional instances, pregnancy will follow this procedure, but it is not recommended for wide use.

Hypoplasia of the uterus, or underdevelopment of the uterus, may be a factor in sterility. Particularly when of a marked degree, as with the infantile uterus, the corpus of the uterus is of equal length or even shorter than the small cervix. Physicians often have informed their patients that they have an infantile uterus and that pregnancy is impossible. The true infantile uterus occurs very rarely. Degrees of hypoplasia of the uterus, on the other hand, are relatively frequent. Patients with small uteri, of perhaps half the size one might expect are by no means definitely sterile, and in many instances have become pregnant following the earliest exposure. On the other hand, hypoplasia may be a factor and may be related to subclinical hypothyroidism. If the clinical findings and the laboratory tests tend to indicate a mild hypothyroidism, improvement may follow long-continued administration of thyroid extract orally, over a period of many months or years. The change and improvement in the size of the uterus are very slow in appearing, but pregnancy may occur.

Estrogens have been used to increase the size of the uterus and are of some value. As a rule, enlargement of the uterus produced by large doses of estrogen is rather temporary, and the uterus often returns to its hypoplastic size after the hormone is discontinued. Smaller doses of estrogen which would not interfere with ovulation, such as conjugated equine estrogen 0.6 mgm. given daily for twenty days, beginning at the end of the menstrual period, may be followed by some slight and gradual increase in the size of the uterus.

Retrodisplacement of the uterus, whether retroversion, retroflexion or retrocession, rarely is an important factor in sterility, because twenty-five or thirty per cent of all young women have a retrodisplacement, mainly of congenital origin. Since the majority of these women become pregnant without delay, the factor of retroversion seems not too important. Yet when one is studying and trying to help the patient with sterility and retroversion is present, there is nothing to lose in raising the uterus and inserting the Smith or Hodge pessary. The pessary must be changed, cleaned, and re-inserted every six weeks as long as it is used. Some patients do become pregnant following this procedure.

Myomas of the uterus may be a factor in infertility, particularly if they are large, of six or eight centimeters in diameter, if they compress the lumen of the fallopian tubes and distort the cornua of the uterus, and if they compress and flatten the endometrium in its cavity. In such an instance, myomectomy is indicated and may be followed by successful pregnancy in an appreciable number of patients. On the other hand, small myomas of two, three or four centimeters in diameter are rarely factors in infertility, and usually should not have myomectomy performed just because they are present. Some authors are more enthusiastic regarding myomectomy.

Adenomyosis also must be a factor in some instances, but this disease is rarely diagnosed clinically. It may be suspected by the history of menorrhagia and dysmenorrhea, and the finding of some enlargement of the uterus. Perhaps a conservative operation of resecting these thickened areas inside the uterine wall may be developed in future years, but few are performed today. Cure of infertility by this procedure will be infrequent, in part because of difficulty in preoperative diagnosis.

Salpingitis may cause complete or partial tubal obstruction. The tubal factor, or tubal obstruction, is the most important single organic cause of sterility. Certainly, partial and complete tubal occlusion are frequent findings in the study of women with sterility. Such partial or absolute occlusion is primarily diagnosed by the Rubin's test (transuterine tubal insufflation using carbon dioxide gas), or by hysterosalpingography, the injecton of radio-opaque water soluble material into the uterus. If the patient suffers acute pain or fever one should never perform these tests. Nor should one ever attempt such manipulation in the presence of sub-acute infections, as indicated by the presence of tubo-ovarian abscess, and particularly in the presence of induration in the broad ligaments and utersacral ligaments and in the cul-de-sac. Only when salpingitis may be diagnosed as being in a chronic stage, as indicated by the palpable adherent ovary without undue tenderness and induration, may one use these tubal patency tests. Often, sexual rest and douching over a period of time is advised before the Rubin's test is performed.

Ovarian cysts and tumors may be factors in sterility, especially if the cysts are bilateral. If the cyst is unilateral and the opposite tube and ovary are normal, perhaps there would be little interference with fertility, except for the alternating ovulation. The ovary containing the cyst may continue to ovulate on alternate months. The normal function of the tube-ovarian relationship would be abnormal in the case of the sizeable ovarian cyst. Surgery is indicated, regardless of the problem of sterility, if a cyst larger than eight centimeters in diameter is present and remains there for a period of six or eight weeks.

Endometriosis is of great importance in sterility. Patients with endometriosis and sterility have retroverted uteri in fifty to sixty-five per cent of cases, commonly adherent to the wall of the rectum and sigmoid, with shotty or nodular thickenings present in the cul-de-sac and uterosacral ligaments, and endometrial implants on the surface of the ovary, invading its interior to form endometrial cysts, small or large, invariably adherent. In patients with these particular characteristic findings, the majority must be sterile. Some, however, do become pregnant, even with the adherent retroversion and large nodulations in the cul-de-sac. Fifty per cent of women who have endometriosis in sufficiently severe degree to require subsequent radical surgery have had one or more children in previous years, so that their pregnancies did not prevent their developing the endometriosis, nor did pregnancy prevent or cure the endometriosis. Either the endometriosis follows the delivery of the children, or it obviously does not interfere with the fertility of all individuals.

The finding of an adherent retroversion with nodular thickening in the cul-de-sac typical of endometriosis and the presence of adherent ovaries, in combination with a history of sterility for one or two years or longer, indicate a probable causal relation to sterility in this instance, provided the husband has normal semen. Good results may follow conservative operative procedures, resecting the endometrial implants, particularly those on the ovaries, and correcting the adherent displacement of the uterus. Pregnancy follows in forty to sixty per cent of such patients, who had been considered sterile.

ENDOCRINE ABNORMALITIES

Functional or endocrine abnormalities in women are factors in some cases. These include amenorrhea, oligomenorrhea, menometrorrhagia, mainly with anovulation, and also anovulatory menstruation. Obviously if a patient has amenorrhea of the primary type, she is most unlikely to become pregnant. If a patient has never menstruated at the age of nineteen, probably no treatment will be successful. In cases of secondary amenorrhea of six months duration or longer, the patient at some previous time having menstruated, withdrawal bleeding may follow stimulation by estrogens or progesterone, and this is sometimes followed by normal cycles, with spontaneous ovulation. Particularly good results may follow if thyroid extract is indicated and prescribed in the proper amounts. The psychological factor is important frequently. In oligomenorrhea (infrequent menstruation, at two, three, or four months intervals), the menses often are preceded by ovulation, though by no means are all cycles ovulatory. If ovulation occurs, the egg will not have been extruded until fourteen days before the subsequent menstrual period, as this is the constant part of the ovarian cycle. Since ovulation with oligomenorrhea occurs at an unpredictable time, it may be difficult for impregnation to be planned, although the basal temperature chart is of help in finding the time of ovulation. Its infrequency and the difficulty of determining the time when it occurs are factors in these cases.

Anovulatory menstruation occurs infrequently in women. Henriksen states that approximately two anovulatory cycles may occur in each twelve, or about two per year, at irregular intervals, whereas ten cycles are ovulatory. No one can predict when the anovulatory cycles will occur; perhaps the emotional upheavals of normal life, changes of climate with vacations, intercurrent illnesses, and other unknown factors are causes of these breaks in the rhythmn.

While anovulation is not a factor in the sterility of regularly menstruating women, ovulation is always confirmed by basal body temperature records, which reassure the patient, and instruct her in the optimum time for conception.

Metrorrhagia, or prolonged and irregular bleeding from the uterus, is usually anovulatory in type, and the endometrium shows only an interval, non-secretory pattern, or endometrial hyperplasia, with no evidence of glycogen secretion, and with swiss-cheese, dilated glands. Such lack of ovulation may continue for many months, but normal ovulatory cycles may return spontaneously, or be aided by curettage, general health measures, thyroid extract, perhaps substitution hormone therapy in some instances, and at times by sedation. Irregular bleeding may be controlled by estrogen or progesterone withdrawal effects, although these withdrawal effects do not, as a rule, produce ovulation in subsequent cycles.

Litzenberg emphasized the beneficial effects of thyroid extract as part of the treatment of sterility. In patients with no obvious organic or functional abnormality, thyroid extract has been given empirically, and many feel with excellent results. Probably the majority treating sterility certainly include thyroid evaluation in all surveys for sterility. The basal metabolic rate, when accurately performed in the relaxed and rested patient, who is not disturbed by the mechanism of the test, remains the best laboratory aid in the determination of mild hypothyroidism. The elevated blood cholesterol may be of value, but this chemical determination is inconstant in accuracy in many laboratories. The lowered protein bound iodine and lowered radioactive iodine uptake are not nearly so accurate with mild hypothyroidism, as are the opposite findings as an indication of hyperthyroidism. Perhaps the clinical judgement of mild or subclinical hypothyroidism is more important than all the tests. However, the education of the public in medical matters often requires laboratory tests. At any rate, it does appear that thyroid extract in dosages of one-half up to two or three grains daily, when given judiciously, with clinical observation of the patient, may be of definite value in the treatment of sterility.

PSYCHOGENIC FACTORS

Psychogenic factors apparently are causes of inability to bear children, perhaps in a considerable proportion of those who complain of sterility. It is difficult for the clinician to understand the psychogenic cause and effect, mainly because at the present time there is no method of determining just which patient has a psychogenic factor, how it can be diagnosed, and how it can be made an entity. Bos and Cleghorn, as psychiatrists, have summarized and have tried to simplify the problem from the psychiatric viewpoint. It is logical to believe that psychogenic factors may affect the endocrine system and the autonomic nervous system, both of which are related to conception. Unusual situations in young women which produce stress, such as social activities of unusual degree, or boarding school, or nurses' training, or on the other hand such dramatic circumstances as feared pregnancy from attempted rape, or complicated emotional situations of fear, grief and hostility, may cause hypothalamic amenorrhea with anovulation. If we assume that psychogenic factors affect nerve stimuli, one can understand these connections, but the more occult effects in an apparently normally ovulating and menstruating woman are indeed difficult to comprehend, and, in fact, are unknown.

The autonomic nervous system possibly may affect the pH of the vagina, the quality of the cervical secretions, or some other unknown characteristics, that may prevent the living sperm from entering the uterus, may cause endometrial changes incompatible with implantation, and may cause spasm in the uterotubal junction, in the tube itself, or at the tubal fimbria. Perhaps congestion, which possibly is related to autonomic nervous system imbalance caused by tension, is another factor.

Personality factors that are considered to affect fertility include emotional immaturity, agressive masculine traits, mother identification, obsessive-compulsive traits and others. How these personality changes could affect fertility is not clear, but it is said that treatment of the personality defects, usually by the psychiatrist, may aid in the cure of sterility. Apparently, sympathetic understanding by the unpsychiatrically-trained gynecologist or general practitioner may aid greatly in some situations, acting as psychotherapy, with subsequent fertility in some instances.

MALE FACTORS

The causes and pathology of infertility as related to the male include congenital abnormalities, such as hypospadias and undescended testicles. In such instances the sperm may not be deposited in the apex of the vagina, or even be produced at all from deficient testicles. A second cause is related to inflammations, such as epidymitis and blockage of the vas deferens caused by gonorrheal infection or, rarely, tuberculous infection. If the ducts leading from the testicles to the prostate are occluded by strictures, operative procedures have been devised to excise the strictures and anastamose the ducts. It would appear at this time that the results are poor, though slightly encouraging, and that the finding of a case amenable to surgery must be very infrequent. In a much larger percentage of men with infertility, there is no obvious physical disease, though the semen analysis shows a subnormal volume, insufficient number of sperm, lowered motility, and less than eighty per cent of normal forms of the spermatozoa. The volume may be as little as one and one-half or two cubic centimeters, the number may be below sixty million per cubic centimeter, when one hundred or one hundred and fifty million are preferred. One sometimes finds forty or twenty or five or one million, or even no spermatazoa at all (azoospermia). The motility may fall below eighty per cent, to forty per cent, twenty per cent, or ten per cent, or even to zero per cent. The normal forms may be decreased to sixty or forty or ten per cent, the remainder showing abnormal forms, such as double heads, giant heads, double tails. These abnormal findings indicate, in degree, a relative or absolute sterility which exists in the male.

Psychogenic factors are important, as regards impotence, when they prevent a husband from having sexual relations. Possibly there are psychogenic effects on the sperm count related to tensions and anxieties, which indirectly affect the hypothalamus, which affects the pituitary, and which, in its turn, affects the testicles.

INVESTIGATION AND TREATMENT: FEMALE

The patient presents herself with the complaint of the inability to have children. Bos and Cleghorn have indicated that the physician should try to determine why this patient wants to have a child, because she really may not want to become pregnant. The history and physical examination are completed, with particular reference to the gynecological system. The blood and urine analyses are checked as a routine, and other special tests are performed as indicated. The patient is examined for organic gynecological disease, encompassing the field from vaginitis and cervicitis to endometriosis and pelvic tumors.

Treatment is carried out as indicated without particular reference to sterility, this being ordinary, good gynecologic care. It is true that the treatment is motivated by the desire to have children as soon as possible. The basal metabolic test is the older procedure, and if properly performed, and the patient is at ease, is of great value, because thyroid dysfunction, particularly subclinical hypothyroidism, is of much importance in all gynecologic functions.

The basal body temperature is charted by taking the temperature at the same time each morning before the patient arises from bed (called the "waking temperature" by the British), by means of a special thermometer calibrated in tenth of degrees, in contrast to the usual thermometer calibrated in fifths of degrees. All temperatures are more accurate when taken by rectum than when taken by mouth, and this method is preferable. Some have advised that the temperature be taken by mouth and that the results are quite as satisfactory. Undoubtedly, in most circumstances, the oral temperature will give reasonable satisfaction, but the difference between oral and rectal temperatures when charted is surprising. Great accuracy is necessary to obtain all the information that is available by this method of study. Some authors, including G. S. Jones, believe that, if the temperature rise is not obvious and sustained as usual, then luteal deficiency is present and the patient should be treated with progestational compounds during this part of the cycle to aid nidation. This luteal defect was stressed earlier by Hughes and his co-workers. The importance of luteal defects, as interpreted by the basal temperature and endometrial biopsy, is not accepted by all investigators.

If the semen analysis is normal, the Rubin's test is performed next. This extremely valuable test was devised by Rubin in 1920 and is performed by the introduction of a small cannula into the uterus, usually metal but may be plastic, with a rubber cork to be pressed firmly against the cervix to prevent regurgitation of the carbon dioxide gas, which should pass through the uterus and tubes and into the peritoneal cavity. Pressure is accurately determined by a manometer which is placed between the gas container and the cannula entering into the uterus. The gas should pass through the fallopian tubes at seventy millimeters of mercury and drop to thirty millimeters. If higher pressures are required for the gas to pass through the tubes before the pressure drops and before one can hear, with the stethoscope on the abdominal wall, the bubbling or whistling of the gas as it passes through the tubes into the abdominal cavity, then a partial tubal obstruction is diagnosed. This partial obstruction may be due to spasm, which is commonly the case, or to kinks or adhesions, or actual inflammation of the fallopian tubes. The gas pressure may be raised to two hundred millimeters of mercury, if necessary, and rarely is raised above this level. If no gas passes through the tubes on three successive attempts at a pressure of two hundred millimeters of mercury (at the same sitting), then one assumes that the fallopian tubes are closed. Sometimes the closure, even at this high pressure, is due to spasm, but more often there is organic disease. A few bold operators have raised the pressure to three hundred millimeters of mercury, attempting to open closed tubes, evidently with some success, but in general one would consider this an excessive pressure, and fraught with risk of rupture of the fallopian tubes. In previous years, other media have been used for insufflation, such as oxygen, and particularly air, but the latter has been associated with air embolism in a sufficient number of cases to make it entirely undesirable. The reason is that the nitrogen in the air is not absorbed into the blood to any degree compared to carbon dioxide, which even in considerable amount, is absorbed rather rapidly by the circulating blood. It is far safer to introduce carbon dioxide gas, and not air, into the fallopian tubes for these studies. If the fallopian tubes are found to be closed, the test may be repeated in one or two months. If they are open the test may be repeated in four months. If no pregnancy has ensued after another four months, hysterosalpingography may be performed, usually on the third test and eight months from the original examination. Some advise that hysterosalpingography be performed on the first occasion. It is important that the most acceptable solutions be used in this procedure. While oily preparations are still being used in some instances, probably the majority of gynecologists feel that aqueous preparations, such as Salpix, are superior, because they are soluble in the blood, and do not act as an oil occlusion, which may occur after the use of lipiodol, iodochloral, etc. If lipiodol is extravasated into the blood stream, an oil embolism in the lungs may cause sudden death. A number of fatalities have been reported following the use of oil preparations, just as there have been a number of fatalities following the use of air.

Both the Rubin's test and salpingography may activate latent infection in the fallopian tubes and produce acute fulminating salpingitis and pelvic peritonitis. This is more likely to occur after the hysterosalpingogram than after the Rubin's test alone. Never should these tests be performed in the presence of any active pelvic inflammation involving the fallopian tubes and ovaries. It is preferable to treat and improve cervicitis before performing them, although the risk with the latter is much less. Pregnancy also contra-indicates hysterosalpingography because of the danger of interrupting the pregnancy and of extravasation into the uterine veins beneath the placenta.

The Sims-Huehner test (the post-coital test) is a simple procedure and of some importance. Sexual relations at approximately the time of ovulation are followed by examination, in one or two hours, of the vaginal and cervical secretions. In the vagina the spermatazoa are usually dead from the acid secretions, but an idea of the number of sperm may be obtained. Microscopic study of mucus aspirated from up in the cervical canal should show fifteen or twenty actively motile spermatazoa per high power field. If no sperm are found, or only a few, and these largely immotile, one would suspect that the secretions of the cervix are inimicable to the spermatazoa, particularly if semen analysis has shown a normal number and normal motility. Such may possibly be related to infection in the cervix or diminished hormone secretion, the latter perhaps a psychogenic effect, with unknown explanation. Infection may be treated with antibiotics or cauterization, and the cervix may be dilated to promote good drainage. Small doses of estrogens, such as stilbestrol one-tenth milligram or Premarin three-tenths milligrams may be given daily with the intention of increasing the secretion of mucus from the cervix. This small dose of estrogen should not interfere with ovulation. Psychotherapy may be considered, but it is difficult to determine which individual may need the psychiatrist's help. Most young women have some degree of emotional disturbance over the problem of pregnancy by the time this test has been performed, because of disappointments, pressures, and urgencies, related to an intense desire to have a child.

As mentioned before, the fallopian tubes may be stretched each four months by carbon dioxide by means of the Rubin's test. Some prefer to use more complicated machines, as advised by Rubin, with a drum and graphic record of the pressures in the uterus and tubes, the oscillations showing contractions. But these may be either of uterine or tubal origin. Many others believe that the passage of the gas into the fallopian tubes with notation of the pressure at which the gas passes through and the lowest level to which the manometer drops, are the important factors, and that the use of the drum and the recording of oscillations are not necessary. Many feel that once the fallopian tubes have been proved to be patent, that repeated tests may further disturb the uterotubal relationship. If the precise answers were known, surely all would follow the same procedure.

SURGERY OF THE FALLOPIAN TUBES

For many years much interest has been focused on the surgical reconstruction of closed fallopian tubes. In 1937, Greenhill reported a statistical survey of the results of 818 surgical operations to open fallopian tubes, and was disappointed to find only six and six-tenths per cent success as determined by subsequent pregnancy. Twenty years later Greenhill again surveyed the problem, and found similar results. Individual authors have reported higher percentages of pregnancies. (Cauwet had twenty-six per cent pregnancies in sixty-nine women, 1958.)

If the hysterosalpingogram shows the tubes are closed at the distal ends, with dilated lumens, one generally thinks this to be the optimum case for surgery. At operation the end of the tube is cut away and the mucosa is sutured to the serosa. Often the tube is split, an effort is made to evert the mucosa far back onto the serosa. At other times the Gomco circumcision clamp may be used without sutures, the pressure sealing the bleeding edges.

The placing of polyethylene tubing into the lumen, leading out through the abdominal wall (usually it cannot be placed through the cornual and interstitial portions of the fallopian tubes), to be withdrawn in two to eight weeks, or the use of a short plastic tube with an attached sac or umbrella of the same material to cover the opened end of the tube, to be removed by re-operating after three months, have been advised by Rock and Mulligan, and others. Their results seem encouraging to them, but there is no general enthusiasm over these procedures.

The problem of the distal end of the tube is its tendency to closure by retraction of the mucosa, stricture formation, and adhesions at its fimbriated end. Surely the answer is in the application of improved plastic surgical methods. The excision of a circumferential portion of the muscularis, followed by everting the mucosa onto the serosa (as with the newer methods of treating the ileostomy stoma), the complete control of bleeding, the use of fine sutures, and delicate technique to prevent surrounding adhesions, should offer better results. Previous efforts, as a rule, have not sufficiently utilized the plastic surgeon's techniques.

When the hysterosalpingogram shows only a hysterogram, with obvious closure of the tubes at the utero-tubal junction, the tendency has been to feel that the situation is more hopeless than if the closure is at the ampullary or distal end. Of course the tube may be obliterated throughout or have multiple points of obstruction, or have obstruction in the cornu and the distal end, with hydrosalpinx formation. Varying degrees of chronic inflammation may be present, which may greatly affect the outcome. On the other hand, the inflammation may be limited to the cornual area, and the distal end of the tube may be normal. More often this local cornual obstruction represents the so-called "salpingitis isthmica nodosa," which is really not salpingitis at all, but adenomyosis, or endometriosis, of the cornual portion of the tube. The cornual obstructions, when caused by the latter finding, or when caused by surgical sterilization of the cornual portion of the tube, may be corrected by excision of the obstructed area, coring out the uterine cornu, and carrying the patent portion of the tube into the uterine cavity by fine sutures which pass through the uterine wall. The incisions in the uterine muscle at the cornua are re-approximated to just the proper degree. Polyethylene tubing is left in the lumen of the tube, extending one inch through the fimbriae into the abdomen, is carried out through the cervix, and is attached to the cervix by suture. This splint is removed after ten to twenty days.

This latter operative procedure offers better results, especially when there is no active chronic salpingitis, than those procedures on the obliterated fimbriated end. When the salpingitis has been severe, as after a ruptured appendix with peritonitis, the results probably will remain poor. Many efforts are being made to form new or substitution fallopian tubes, but none have seemed successful as yet.

INVESTIGATION AND TREATMENT: MALE

In the investigation and treatment of the male, first the general health is inquired into and if the patient is not excessively overweight or underweight, if he has reasonable health habits, then the semen analysis is all that is required. If the count shows insufficient sperm, with lowered motility and abnormal forms, a clinical examination, basal metabolism, and blood count are indicated. Therapy may include vitamin and thyroid therapy. Alcohol has been incriminated in some instances as a spermotoxin, tobacco in a similar manner has been suggested as a vague cause of infertility, and lack of vitamin A, B or C may possibly have come connection (it appears that vitamin E is of no real importance because of its widespread distribution in normal foods). An example of possible vitamin effects was given to the author by Doctor Norman Miller some years ago when he recounted the story of a prize bull bought by the State of Michigan to inseminate the heifers of the state and so to improve the quality and quantity of milk which they produced. After the bull attempted a number of impregnations, without results, examination of the semen showed a marked deficiency. An eager investigator found that the vitamin C content of the blood of the bull was markedly lowered. Soon after the administration of large doses of vitamin C, the bull promptly became fertile and impregnated many cows in Michigan, with great success for all concerned. That vitamin C may be of value in men has not been proved, but it is doubtful that it could be harmful. Others have preferred vitamin A or vitamin B, or combinations. More research is necessary before the importance of this therapy is made clear.

Another approach to treating the deficient male includes hormone therapy. The testosterone-rebound phenomenon was presented by Heckel some few years ago, in which the patient with low sperm count is given testosterone, usually as testosterone propionate twenty-five or fifty milligrams intramuscularly three times weekly, for three or four months. This hormone causes the sperm count to drop to zero. After a few months, the count rises to above the pre-treatment level in one-third of the cases, to the same level in one-third of the cases, and remains permanently lower than before treatment in one-third of the cases. Apparently, in those whose count is raised, the chance of pregnancy is greatly improved. There is possibly a question as to the wisdom of using this therapy, but several investigators have presented encouraging results. Some years ago equine gonadotropin was advised for stimulating the gonads of the male, to say nothing of the female, and it was thought that the sperm count could be improved by injections of this hormone. The general opinion has seemed to be that such medication is of no value. At one time this author thought there was a real beneficial effect from equine gonadotropin, but very careful semen analyses are needed for further evaluation. Variations in semen counts may have many explanations.

Mental and emotional factors are always mentioned, and proper physical exercise and emotional relaxation are advised for men with diminished spermatazoa.

It is at present believed that azoospermia, or complete absence of spermatazoa, involves absolute sterility in the male, that the condition can never be improved, and that the result is permanent. Low sperm counts may improve of their own accord, being affected by temporary illnesses, sexual excess and unknown causes. The only known direct causes of low sperm counts or azoospermia are mumps orchitis, which is a very serious disease in young boys, and, hypothyroidism. The former may cause azoospermia with irrevocable change. Hypothyroidism may cause low sperm count, with improvement to normal if properly treated.

The only possible improvement in azoospermia is the relief of blockage of the vas deferens, when such is the cause of absent spermatazoa, by resection of the stricture and re-anastomosis. This operation has been performed in rare instances.

ARTIFICIAL INSEMINATION

Insemination is classified as A. I. H. (artificial insemination of the husband's sperm) and A. I. D. (artificial insemination of donor sperm). Some specialists in the field of sterility have felt that when the sperm count is low in the husband, insemination of this weakened semen may aid in conception. But the majority in this field tend to think that insemination of the husband's sperm is of little or no value, that if the sperm are not strong enough to penetrate the cervical canal, then they are not potent enough to fertilize the ovum in the fallopian tube. The use of donor insemination, only in cases of azoospermia or oligospermia in the husband, has received considerable interest for a very long time, and increasing interest in recent years. It is performed in the large cities with much more matter-of-factness than in less populous areas. Religious mores enter into the practise, as the Catholic religion forbids insemination. There is some question as to the legality of the procedure, and as to the legal position of the progeny, should the origin ever become known. The religious and legal questions deter many, but there are other distractions. The first is that the husband, who may seem to accept this method of insemination without apparent reluctance, later may bitterly resent this procedure and may develop serious psychological difficulties. At least this may be the situation in some instances. Unless one can be certain that the husband has no secret reservations and whole-heartedly favors donor insemination, the physician will do well to delay his decision. Some wives may think they favor this procedure, but subsequently change their minds, and experience great uneasiness, either having some moral reservations or some doubts about the blood lines involved. These emotional factors may be more important than the religious and legal points, and should cause this method of donor insemination to be used only with great care and discrimination. The procedure is a simple one, consisting of transferring the semen from a clean bottle to the upper vagina about the cervix with the medicine dropper. The patient usually remains supine for one hour. The time for insemination may be judged by the temperature graph. Usually it is performed on the twelfth, fourteenth and sixteenth days of the cycle, if the low point of the temperature occurs on the fourteenth day.

SUMMARY

In the experience of the writer, thirty per cent of patients treated for sterility became pregnant. Seventeen per cent of those who made one visit only, and sixty-five per cent of those who completed one year or more of study, and performed every test and treatment required, became pregnant. The younger wife had a greater chance of success. Of those twenty to twenty-five years of age, forty-three per cent became pregnant. Of those thirty-five to forty years of age, only ten per cent became pregnant. Sixty per cent of all patients have had some gynecologic abnormality, varying from metrorrhagia and cervicitis, requiring treatment, to retroversion, myomas and endometriosis. About ten per cent of sterility patients may, after thorough study and investigation, require major surgery. Reconstruction of the fallopian tubes has not been successful in my experience, a very small percentage of the women concerned becoming pregnant. Endocrine therapy is of little value for sterility in women, and is rarely indicated. It also seems of no great value in men. Thyroid extract is a most important product; it stands apart as a hormone. Of the husbands of our patients studied, one-third had sperm counts above sixty million per cubic centimeter, one-third had sperm counts from forty to sixty million, and one-third had counts below forty million. Five per cent had azoospermia and were completely sterile.

Ordinary and proper gynecological care, with correction of minor or major abnormalities, efforts to maintain patency of the fallopian tubes by repeated and appropriate procedures, and observation of the semen content, with treatment when indicated, comprise the present therapy for sterility. These measures are not complicated, and the results are encouraging. Psychogenic aspects possibly are of great importance, and more effort must be devoted to understanding the role of these factors.

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CHAPTER XV

The Menopause

Menopause means the cessation of menses, a permanent cessation of menses, and not a secondary amenorrhea in which menstruation may be re-established spontaneously or by treatment, because in the true menopause, menstrual function cannot be re-established. The average age of this permanent cessation is forty-seven years, although not uncommonly menstruation persists until fifty-four or fifty-five, and it may cease in the early forties, less often in the thirties and rarely in the twenties. One cannot determine that a woman's menstrual periods have ceased permanently unless the vagina has become quite thin and only oval and round parabasal cells are shed into the lumen. On the other hand, in many instances, probably half of cases, the vagina does remain fairly thick with a full estrogenic effect for a considerable period of time before the atrophic changes appear. When the menses have ceased permanently, ovulation will not occur again, but as long as the vagina remains thick, or at least for quite some time, one knows that ovulation could occur, to be followed two weeks later by menstruation. Fertility, though greatly diminished, is not completely absent for some indefinite period of time, at least until the atrophic changes in the vagina have appeared.

MENOPAUSAL SYMPTOMS

Menopausal symptoms occur in a large percentage of women, probably seventy-five or eighty per cent. These symptoms may be divided into two categories. In the one instance the vagina remains thick, and the fresh preparation shows an essentially full estrogenic effect. In these cases, the patient may complain of hot flashes, anxiety, nervous tension, and a tendency to depression. These complaints are not caused by lack of estrogenic hormone here, but are related to the stresses and strains of life and the individual emotional instability of the person. Strictly speaking, these are not menopausal symptoms, but are nervous symptoms such as may occur at any time of life in man or woman, and are not caused specifically by the cessation of menses or the decrease in hormones. It must be said that there are some psychological disturbances from a woman's fear of old age or the loss of her sexual attraction. This is a readily understood reaction, and again is not a strictly menopausal symptom.

The true menopausal symptoms can develop only when the vagina has become thin and when the cells that are shed are of the round and oval shape with relatively large nuclei, being immature cells from near the basal layer. These parabasal cells indicate a marked decrease in estrogenic hormones.

The symptoms of true menopausal origin include primarily the hot flash, and secondarily, nervousness, sleeplessness, various aches and pains, backaches, numbness and tingling, arthritis, arthralgia, headaches, and other vague complaints. The most characteristic of all of these symptoms is the hot flash. The hot flash, or hot flush, is a feeling of warmth that spreads up over the chest into the neck and face, with associated nervousness and self-consciousness, which may recur at frequent intervals or only a few times daily. In some instances, the patient complains of these symptoms only during the night.

The hot flash, while characteristic of the menopausal symptoms more than any other, may be truly menopausal or may be of strictly nervous origin. This is to be determined by the thickness of the vagina, and the vaginal smear. If there is a full estrogenic effect, then certainly no improvement is to be expected from the administration of estrogenic hormone, and the symptoms are assumed to be of nervous or anxiety origin. This is a most important differentiation, because the tendency has been to treat any woman complaining of hot flashes immediately with estrogen, regardless of her age and regardless of the presence or absence of her menstruation. When hot flashes and nervousness occur before menstruation has ceased, they are never of true menopausal origin and never due to a lack of estrogenic hormone, because if there is sufficient hormone to allow menstruation to occur, then there is sufficient to prevent any hot flashes due to lack of hormone. The treatment of patients with vague nervous complaints at any age with estrogens, and especially in the so-called "grey zone" between the ages of thirty-seven and forty-seven years, is improper in the minds of most gynecologists.

TREATMENT

The treatment of the patient with hot flashes and nervousness, associated with a full estrogenic effect, begins with tactful inquiry into the patient's home life, daily situations, financial, sexual and familial difficulties. The main effort is to clarify the problems so that the patient may see them more easily. This mild psychotherapy is of tremendous importance in these cases. The mere knowledge that the symptoms are not of truly menopausal origin, that there is no lack of hormone, immediately clarifies the problem for the patient. Sympathy and advice, though the latter is minimal, are helpful in treatment. The addition of mild sedation for temporary use, with dosage adjusted for the individual patient, adds to the proper treatment in these cases.

On the other hand, in the patient with the true menopausal symptoms associated with the atrophic vagina, the primary treatment is with estrogenic hormone. Since thirty years ago, when theelin (estrone) was first isolated by Doisey, great strides have been made in this field. From the injectible theelin, the injectible estradiol benzoate, oral stilbestrol, and the conjugated estrogens, and even pellet implantation, much success has followed. While injectible intramuscular hormone is continuing to be used, and is quite satisfactory in its effects when given at intervals of ten to fourteen days, yet the same results may follow the oral estrogens with less expense and without the slight risk of contamination or reaction from the hypodermic injection. Pellets of estradiol or estrone may be implanted in the subcutaneous tissue to be absorbed slowly over a period of many months, and often over a period of two years (in the case of the former), which allows the estrogen to be absorbed continuously. The results of pellet implantation are quite satisfactory, but are better when used in the hysterectomized patient, because of the possibility of overstimulation of the endometrium with subsequent bleeding. The rare occurrence of breast cysts after pellets is of some concern. The standard therapy of the day is that of the oral estrogen, and includes most popularly stilbestrol and its derivatives, esthinyl estradiol, and conjugated equine estrogens (estrone sulfate and equilin, marketed as Premarin). With any estrogen, the smallest dose is preferred that will give good results; one may prefer 0.3 milligrams Premarin daily over a period of many months or several years. In some, 0.6 milligrams Premarin daily is given, especially if hysterectomy has been performed. In rare instances, 1.25 milligrams Premarin daily is prescribed, but this latter dose commonly causes breast engorgement and abnormal bleeding if the uterus is in-situ. Some have preferred to use the hormone cyclically, giving it twenty days out of every twenty-eight days, following the more normal cycle before the menopause occurred. However, this allows the sustained level of estrogen to drop sharply and causes some recurrence of symptoms before the hormone is started again.

A second hormone that may be used is testosterone and its derivatives, which does reduce the symptoms of the menopause. This is effective by depressing the overaction of the pituitary gland, which is producing an excess amount of FSH, now the so-called menopausal hormone, and which may be the cause of the menopausal symptoms. The symptoms seem more likely to be due to the removal of the tonic effect of the estrogen on the arterioles of the body and on the sympathetic nervous system over a period of thirty years. At any rate, the testosterone is efficient, but if used over any period of time, even in relatively small doses, it is virilizing, the degree depending on the dose, and, therefore, not to be preferred.

The combination of estrogen and testosterone has been advised in the past few years, the first thought being that a combination occurs normally in the woman, and secondly that the testosterone might depress the estrogenic effects that over-stimulate the endometrium and cause bleeding, and that the estrogen might prevent the testosterone from producing a masculinizing effect. Thirdly, the combined use of hormone has been thought to aid protein metabolism and prevent decalcification of the bones, and thus help the general health and vigor. Actually, it has been found that the amount of testosterone necessary to neutralize 0.6 milligrams of Premarin (estrone sulfate) is about twenty-five milligrams of methyl testosterone. If this combination is given, within a very short period of time rather marked virilism will occur. Consequently, the estrogenic activity cannot be overcome for any practical purpose. If five milligrams of methyl testosterone is combined with 0.6 milligrams of Premarin, one would think that the stronger estrogenic effect would neutralize the androgenic effect, but observation has shown that the androgenic activity is not diminished regardless of the estrogen. Two or three months of such therapy will show definite though slight masculinizing changes, with enlargement of the clitoris, increased growth of hair on the face and upper lip, and the appearance of acne of the skin. These are undesirable effects, and makes the combination impractical.

Sedation is an important method of treating menopausal symptoms. Phenobarbital, gr. 1/4 t. i. d., or butisol sodium, gr. 1/4 t. i. d., may give remarkable relief of hot flashes and the nervous symptoms associated with this syndrome, whether they are truly menopausal or whether they are entirely functional. Of late, the practice of using various tranquillizers, of which there are many, has an entirely similar effect to that of the ordinary sedatives. Perhaps some of them are better, but the majority are similar. Vitamin A has been suggested by several as a treatment of menopausal symptoms. Its use is equivocal and probably ineffective.

X-ray therapy to the pituitary gland has been reported as giving excellent results, the theory being to depress the over-secretion of FSH from the pituitary gland. In a small series treated with x-ray to the pituitary, compared with another small series in which the light of the machine was turned on but the actual x-ray therapy was not given, the results were equal. This is an example of the tremendous functional element in the menopausal symptoms present in essentially all cases.

Undoubtedly, there are many other approaches to the treatment of this condition, including the psychologic and hypnotic, but the specific treatment for true menopausal symptoms due to an absence of estrogen is the replacement of estrogen.

EFFECTS OF ESTROGEN ON GENITAL TISSUES

The administration of estrogenic hormones orally, subcutaneously, by pellet implantation, or sublingually, is similar, in that a growth effect on the genital tissues, including all of the genital tissues but most sensitively portrayed by the vagina and endometrium, is obvious after treatment for two or three weeks. The endometrium becomes thicker with the proliferation of an interval non-secretory type, and over a long period of time the constant stimulus of estrogen in a moderate dose, or the use of a very large dose of estrogen, produces tremendous thickening of the endometrium with the development of swiss-cheese glands with no evidence of glycogen secretion, the typical picture of endometrial hyperplasia. As the estrogen is given over a considerable period of time, perhaps one month or three months or more, the level in the blood tends to vary, and bleeding from the endometrium is rather frequent. In fact, postmenopausal bleeding today occurs more from the use of estrogenic hormone than from any organic disease. This does not obviate the utter necessity of studying every patient carefully for malignant disease that might produce the same symptom of bleeding. Since bleeding occurs so frequently with the continued use of estrogen, one is prone to reduce the dose less and less, so that the smallest amount is given that will alleviate the symptoms. This is also approximated by observation of the thickness of the vagina and the vaginal smear. Every effort is made to avoid excessive dosage, so that the standard treatment of menopausal symptoms may be by the use of stilbestrol, 0.1 or 0.5 mgm. daily. With the conjugated equine estrogens, the most frequently used dosage is 0.3 mgm. daily, but 0.6 mgm. may be used. In rare instances, 1.25 mgm. or 2.5 mgm. may be indicated. Some have advised that treatment be interrupted for eight days out of each twenty-eight days to allow the endometrium to involute as much as possible, and attempt to avoid the over-stimulation. However, the continued use of very small doses of hormone gives a much smoother result as regards alleviation of the symptoms.

The sensitivity of the endometrium does vary greatly from patient to patient, and bleeding in some cases may follow the smallest doses. In these, one tends to avoid any estrogenic hormone and rely mainly on sedation. Actually, any woman can live with her menopausal symptoms, if there is a strong reason for her to do so.

When bleeding has occurred after the use of estrogen, one discontinues the estrogen; if the bleeding abates in five to eight days, the patient may return to the hormone after a few weeks rest, usually in smaller dosages. However, if the bleeding continues longer than two weeks, the patient always must have diagnostic curettage. The endometrium commonly shows degrees of endometrial hyperplasia, and not infrequently forms of atypical hyperplasia, in which the glands are unusually close together in certain areas, and with areas of piling up of the glandular epithelium. Certain irregularities that become suspicious of pre-malignancy or early malignancy may be present. Usually with further observation, these changes in the endometrium evidently are caused by the estrogen alone and disappear, with removal of the hormone. These peculiar effects in the endometrium cause one to be concerned at times that estrogen possibly can be pre-cancerous, and yet there is no definite proof that this hormone does cause cancer of the endometrium. A few well-documented cases are available in the literature in which cancer has developed following treatment with estrogens, but they number only a dozen or so cases, and when compared with the millions of women treated they are too few to be of any significance.

Curettage for bleeding, when it has continued beyond a certain time, not infrequently reveals endometrial polyps. These polyps are more frequent than those occurring in the average postmenopausal patient not treated with hormones, although it must be pointed out that polyps of the endometrium after the menopause are really quite common. Yet, it does seem that there is a relationship in the formation of these polyps to the administration of hormones. On a few occasions, one sees extraordinarily large polyps develop relatively rapidly when the patient is under treatment with estrogens. Microscopic examination of the polyps removed from the endometrium under these circumstances following estrogenic therapy usually reveals a marked and typical form of endometrial hyperplasia with swiss-cheese glands and marked hyperplasia of the epithelium. The stromal cells are active, and there may be occasional mitoses. In some instances within these polyps there is adenomatous hyperplasia with marked proliferation of the glands, very closely approximated with extremely little stroma between them, and various areas of papillary enfolding and atypical cells suggest premalignant changes. Again, as a rule these changes are reversible, are due to the hormone, and not neoplastic of themselves. As to whether they may have some final neoplastic effect is unknown. The development of adenocarcinoma of the endometrium from the long continued use of estrogen must be extremely rare, if it ever occurs. But the possibility is an important one that is to be considered by every conscientious practitioner prescribing estrogens. That the endometrial tissues are extra-ordinarily responsive and grow readily due to the estrogenic hormone are well known. That strange, atypical changes occur with the influence of this hormone also is clear. As to whether after the most extreme atypical changes, an autonomous new growth may develop and continue of its own volition to become an invasive malignant tumor has not been proven at this time.

Following the use of estrogens after the menopause, the uterus enlarges in degree, and sometimes to an alarming degree. If the dosage is kept quite small in the average case, there may be little or no enlargement. With moderate or relatively large doses, remarkable increase in the size of the uterus may occur, and these cases are more prone to bleeding.

Myomas of the uterus may be a contraindication to the use of estrogens, because certainly they are responsive to estrogenic hormone, and their size and rate of growth is dependent on the estrogen present. The great tendency is to hope that the patient may reach her menopause, and that the myomas she has will regress in size and become asymptomatic. One cannot expect any regression if the patient takes any appreciable amount of estrogen, and even relatively small doses may maintain the size of the tumors. In these cases, as a rule, it is better to avoid estrogenic therapy.

Endometriosis, whether involving the walls of the uterus, as adenomyosis, or the ovaries and pelvic peritoneum, atrophies and symptoms abate when the true menopause arrives, and when the estrogens cease to be produced. The implants in the cul-de-sac and uterosacral ligaments and the chocolate cysts of the ovaries recede, and the exquisite tenderness and pain disappear. The simultaneous appearance of hot flashes and other menopausal symptoms are a mixed blessing. Administration of any but the smallest doses of estrogens produces a recurrence of pelvic pain. Treatment is to be given with greatest care and with continouous observation. Many physicians will avoid estrogens completely in the patient with endometriosis and use androgens sparingly.

DURATION OF SYMPTOMS AND TREATMENT

The duration of the menopause is so indefinite and variable from patient to patient that one cannot prognosticate its course. The menopausal state actually continues indefinitely once it has arrived. The atrophy of the vagina and vulva, the atrophic changes in the uterus and ovaries, the thinning of the skin, and the loss of subdermal elastic tissue, the loss of the subdermal fat, changes in the mucous membranes of the nasal and urinary tract, are all factors in the menopause which are continuous and never to be improved upon of their own accord. It is the beginning of senility in the woman. Nervous symptoms, including hot flashes, may be absent completely and indefinitely in ten per cent to twenty per cent of cases, may occur in moderate degree over a year or two or less in thirty to forty per cent of cases, but many of the patients, and a very appreciable percentage, continue to have hot flashes, perhaps less severe, until they are very elderly, even into the nineties. These hot flashes may be relieved by the administration of estrogenic hormone. With good psychology, patients can learn to ignore hot flashes or live with them. With poor psychology and less stability, they may present quite a problem for many years.

There are more than just the symptoms of nervousness and hot flashes, and the other vague complaints of the menopause, that are to be considered in the treatment of the postmenopausal woman. The thinness of the vagina, with the subsequent atrophic vaginitis, and the necessary dyspareunia that is to follow, mean the interruption of normal sexual activity in the average woman after the menopause. The changes in the skin of the extremities and face, particularly due to a lack of estrogen, are very definite and obvious. The changes in protein metabolism, which are less concrete but apparently important, and the changes in bone metabolism with absorption of calcium, may affect the health of the woman more importantly than her hot flashes. For this reason, the judicious use of estrogenic hormone in the absence of any tumors, in the absence of endometriosis, which may be stimulated by the estrogen, in the absence of a very sensitive bleeding uterus, may be followed by an important sense of well-being for the patient as an overall treatment, and is to be considered over a period of indefinite time. Does this mean that a woman should take estrogenic hormone as long as she lives? Does it mean she should take hormones for ten years, or for five years? That is a question that can never be settled in the individual case, and is never to be met directly, because the administration of the hormone is to be determined only for an immediate period of time, after which it is to be reconsidered. There are some women who accept the menopause with gracefulness and pleasure, who apparently are not improved further by the administration of small doses of estrogen. There are many others who will note the benefits and improvements after treatment with great appreciation, and will be well-treated with the estrogens over a long period of time. These patients always are to be under medical observation, with reconsideration of the situation as determined by the personality and psychology of the patient, and by the physical examination and the symptoms.

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CHAPTER XVI

Gynechiatry

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The title of this chapter will not be found in a dictionary. It is simply meant to imply the treatment of some usual emotional reactions occurring in women.

The average woman is a most courageous person — well integrated, and capable of withstanding repeated and serious troubles, both physical and emotional. It would hardly seem necessary to emphasize the importance of allowing the patient to talk about her troubles, nor should we need to suggest that there is an entire person containing those offending female parts. However, these truisms are often overlooked by the busy practitioner. To help him avoid these omissions is our purpose.

The actual cause of most mental illness is unknown. There are many textbooks on psychiatry which adequately cover the various etiological theories. The vast descriptive literature covering the psychoses and neuroses is available in all medical libraries. We will try to point out some common problems encountered in the practice of gynecology and to suggest solutions which have been helpful to us.

There are few areas in human existence which are so fraught with misinformation, so full of fact and fantasy, fear and folklore as that of sexual activity. This area is confused by misinformation learned in childhood, facts from one's own experiences, fantasy as one would like to imagine things to be, fear of too much and fear of too little, with a coloring of folklore distorting it all. It is a miracle that so many people are so well adjusted to the absence or presence of sexual activity. We bring to our practices our own attitudes, prejudices, and feelings, tempered poorly or well by a hoped-for objectivity. It should be an humbling experience to know then that our patients are expecting us to serve as the court of last appeal in matters so shaded by emotion. Our greatest service can be rendered to our patients by attempting to determine what their problems are and what they mean to the patients. It is often the experience of a parent to learn, often too late, that those circumstances he feared most did not bother his child at all. So it is we must know that our patients' problems may be entirely different from our own. We have found that our best results have come from allowing the patient to voice her fears and anxieties and then encouraging her to expand on the believed consequences. This simple method of expose helps dispel many superficial but crippling attitudes. Much is known about sexual behavior, but it still remains a very personalized "sacred cow."

In our culture the mores emphasize the concept of virginity until marriage and all sorts of means are employed by all sorts of people to assure its survival. These pressures vary from a simple logical acceptance of the concept of virginity to promises of certain and swift retribution, followed by an eternity of misgiving. There are other self-imposed restrictions, some quite natural and normal, others bizarre in their direction and intensity. Whatever their origin or rationale, it is asking a great deal of the average individual to live a completely abstemious life for years, and then suddenly to break through all her own defenses and become a satisfactory sexual partner. Many women do — mirabile dictu! — but too many are caught in a morass of misinformation. In an attempt to help these patients help themselves it becomes necessary for us to recognize that they may have different concepts than we do. We must learn from them wherein they are discomfited, embarrassed or otherwise non-functioning. Sometimes a very simple explanation will serve to allay fears. In other cases this quest for the cause of the difficulty may require more time than one can afford. If this is so, the physician can help the entire treatment process by the way in which he refers his patient to a psychiatrist. The method is very uninvolved but tremendously important. First, tell the patient what your findings are from a physical standpoint, and what you intend to do or not to do about them. Then tell her in non-technical terms that you also believe she would benefit by discussing her problems with someone whose principal interest lies in that field.

This may seem to be over-simplification, but you have answered her questions concerning her complaint pattern, you have given advice which is helpful, and most importantly you have not told her directly or indirectly that you consider her a neurotic or that there is nothing wrong with her. This is probably the most common offense of the busy practitioner — to tell a patient who has complaints that there is nothing wrong with her. It is insulting, to say the least, and too often is really an expression of his own impatience with so-called functional elements. Recognizing that all of our patients are going to die some day, we really should be pleased to discover an absence of demonstrable organic disease. Our ability to convey this good news to our patients will have a tremendous therapeutic effect. Communication between patient and physician is often more difficult than it would seem.

We are busy people and entirely conversant with our subject. Accustomed to technical terminology we often forget to use the simplest synonyms possible in talking to our patients. We forget, too, that no matter what outward appearance is presented, our patients are confronted with a new situation and are therefore, normally, a little frightened. None of us perform at our best under stress, nor do we like to appear stupid, ignorant, or afraid. Patients often leave the doctor's office with many questions unanswered because of their own embarrassment or the physician's overuse of technical terms. Much folklore can be dispelled by a simple verbal give-and-take in words anybody can understand. A wide vocabulary is a great asset to anyone but particularly to a gynecologist who must use fine shadings of language to question, instruct, and reassure more or less frightened patients. On occasions it becomes necessary to reassure fearful husbands. One finds that many of them are extremely apprehensive about their wives, and here again it must be borne in mind that the simplest language is the most effective. Some husbands are totally indifferent, while others insist upon knowing every detail of the procedure proposed and the potential outcome. In still others it may be advisable to talk to the patient and the husband together so that misunderstanding can be avoided. This is a highly individualized matter and should not necessarily be a routine procedure. Some physicians effectively use diagrams to clarify certain points, particularly anatomical, but these, too, must be kept uncluttered by trivia, unencumbered by the irrelevant.

Frigidity is very rarely due to genito-urinary disease. It is most commonly the end result of attitudes and feelings garnered, distorted, or bruised in the process of growing up and living. Some of these attitudes were firmly implanted by parents, some by acquaintances, some were endogenous, and still others are the direct result of unhappy sexual experiences. In our attempts to treat the symptoms of frigidity (and in many cases painful intercourse is an expression of frigidity), our best results have come from taking a complete history of sexual activity, performing a complete physical examination, then discussing with the patient some of the reasons for her failure to respond. Sometimes the husband is at fault. This may be due to his ignorance, embarrassment, selfishness, callousness, or a combination of these and other factors. Bad breath or poor personal hygiene have contributed to poor sexual response. Sometimes the husband is not at fault, as witness the meticulous, self-centered woman who considers herself unassailable but presents a constant challenge to a normal, but now frustrated husband. In this connection one knows that an apparent inability to give the wife satisfaction often causes chagrin and feelings of inadequacy in the husband. These are sometimes compensated for by extramarital excursions with their potential for unhappiness. Gentleness and patience are often required over a long period of time to overcome some blocks to satisfactory sexual relationships. Fear of pregnancy is a real deterrent to sexual enjoyment. This symptom may be quite complex or it may be a simple, but real, anxiety. The choice of contraceptive advice given must, of course, respect first of all, religious teachings. Then the consideration must be given to the individual. We will too often give careful and full instruction on the use of a diaphragm and discover later that the patient's finer sensitivity is such that the very act of insertion arouses a sense of debasement so strong that she will not use this method. A male type of contraceptive is often necessary in instances of this nature. However, some men refuse to use condoms or are rendered impotent by them. Here, as with all verbal help, we must remember that we are advising with two people other than ourselves who have their own personalized prejudices and whose problems may seem silly to us — but to them they are paramount.

In guiding patients to sexual compatibility it must be remembered that this type of adjustment makes many demands in the realm of give and take. An argument in the course of the evening meal is not necessarily conducive to connubial bliss. Digital stimulation of the clitoris by the male could be quite offensive if the female had had a problem of masturbation. Some women are spontaneously more aggressive sexually than others, and this could cause a degree of impotence or premature ejaculation in some males. There are too many ramifications to cover completely here, but we have found that a simple understanding of conflicting areas, with uncomplicated suggestions for acceptance of differences and ultimate compromise will aid most people. Occasionally a patient who finds herself frigid with her husband will in various ways attempt to get the physician's permission to engage in extramarital activity. This can never be condoned, for obvious reasons. Furthermore, if she were psychologically organized in such a manner to be able to indulge herself she would not be asking your permission. This situation can be handled poorly or well: poorly, by implicit scolding or disapproval; well, by strengthening the patient in her determination to do what her conscience dictates as right.

There are so many drugs and hormones on the market that it becomes necessary for the physician to evaluate carefully the clinical results as compared to the pharmaceutical house claims. It has been said that it is practically impossible to evaluate the therapeutic effect of any medication given to any patient by any physician. If this is so, we should be extremely skeptical of the rather remarkable changes brought about by the administration of any hormone or drug. Most patients want desperately to believe they are being helped. We must not delude ourselves, but must be as scientifically objective as possible. In general it is better to use a few drugs with which one is familiar than to be constantly experimenting with every new drug offered. When we do use drugs it is important to give enough to get a desired result. One and one-half grains of a barbiturate is not likely to give the average woman a good nine hours sleep the night before surgery. Too much of any drug can cause a toxic reaction and obviously should be avoided. Too little is ridiculous. Some drugs, innocuous in small doses, can if used to excess be stored up in the body and result in deleria. The so-called tranquilizers are a good case in point, for when they are used in moderation and as properly indicated they are quite helpful. If used injudiciously, many toxic symptoms can result. The outstanding symptoms of any delirium are fear and confusion. Delirium tremens is not caused by the too rapid withdrawal of alcohol but rather by too much alcohol over too long a period of time and by the ingestion of too little food. Chronic alcoholics may develop deleria under the stress of emergency surgery. When deleria do occur the treatment is clear: withdraw the offending medication, supply fluids, food, and vitamins by the most expeditious route. The use of a sedative with low toxicity may be required. If elective surgery is necessary on a patient who has a problem with alcohol, there should be an enforced period of abstinence with general supportive care for a minimum of two weeks before operation.

Obesity, from whatever cause, is most successfully treated when the patient is motivated to lose weight. The physician has the relative authority of his position to enforce the order to get rid of the excess pounds. However, this is many times not sufficient. If the patient herself can be persuaded of the need for this effort the rest of the way will be much easier. One of the greatest drawbacks is the discouragement felt when the pounds fail to melt off in that crucial first week or so. There are many reasons for some women to over-eat, but it is a fact that many do. These patients may be helped, especially in the beginning by a diet low in calories, but high in volume. The process becomes easier if the patient is not hungry all the time. Some drugs are useful in this area, but they are not without potential dangers. If the reducing diet is suited to the individual and her needs, the chance of success is much greater. The will to reduce is the real key to attainment of weight loss.

The folklore surrounding genito-urinary functions is great and often deep-rooted. Some of the more common ideas are perpetrated by older women and like most folklore have a modicum of reason for their belief. It is true that some patients have developed a psychosis after delivery of a child. It is equally true that some patients have developed a psychosis after not delivering a child. In fact, most psychoses occur in women who do not have babies. It seems we are hardly justified in retaining the concept of a post-partum psychosis.

When gynecological surgery is necessary there are many questions which, if answered properly, will smooth the patient's way. Folklore has it that many women become frigid after hysterectomy, or that they might "lose their minds." A discussion of the facts will ease a tremendous burden for many women.

Masturbation is a fairly common manifestation of growing up. It has also been named as a cause of insanity. Excessive masturbation is sometimes found as a symptom in certain mental illnesses. There are persons with psychoses who have never masturbated. If masturbation were a cause of psychosis, the incidence of mental illness would surely be greater than it is.

Sexual deviation is usually thought of by most people as a trait peculiar to other people. We physicians must accept our patients as they are, and help them to live more comfortable and happier lives. Before a sexual interest is labeled perverted it is a good idea to explore the limits of normal or usual. Some men find an excessively fat woman sexually repulsive. Others link an emaciated female with ill health and impending death and are revolted. Both are socially acceptable, though they may be individually nauseating. We must help people to help themselves and withdraw the imposition of our attitudes upon our patients.

Sexual drive or interest obviously varies with the individual, and most normal or usual people will adjust their sex pace to each other's needs with understanding and patience. With this in mind the problem of advice as to sexual activity postoperatively or in the presence of disability becomes more difficult. Your instructions will probably be followed more closely if you do not decree needless abstemiousness.

A relatively sudden loss of sexual drive warrants further investigation, as does the onset of excessive interest especially with poor control. These may be but symptoms of a more severe disorder, such as a depression or an elation. Occasionally an increased sexual preoccupation is found in the geriatric patient, but this is usually self-limiting.

We are often asked by patients to give their daughters sex instruction. By the time this request is made it is usually a little late. The time for a mother to give her daughter any kind of instruction is the first time a question is asked. If the mother has been able to answer the child's questions simply, directly, and to the point, and then has had the good sense to say no more, that child will ask her mother the next time a question arises. If, however, the mother becomes embarrassed, uncomfortable, and scolds the child, or demands to know whatever gave her that idea, instruction is over, school is out! Few of us, young or old, want to bring down righteous wrath on our heads, so we quit asking mother and ask the playmate. The first questions are simple and easy, and the simple and easy answer is all the child wants at that time. For example, if the question "Where do babies come from?" is asked, the simple answer "from their mothers" will suffice. The birds and bees are too complex here, unwarranted, and unwanted. However, if the mother has been unable to help her daughter, we physicians shall have to pick up the pieces and try to minimize misinformation and direct our instruction toward those areas the child is unclear about. Then we, too, must be able to answer the questions simply, directly, and to the point, without confounding the child with technical jargon.

The same basic idea holds when the doctor is called upon for premarital counseling. The positive, healthy aspects of marriage must be emphasized, with the patient being allowed and encouraged to ask every question in her mind, no matter how seemingly insignificant. Here is a wonderful opportunity to help people to live happier lives.

There are physical sensations accompanying menstruation and there are premenstrual tensions. Some women have severe cramping; others have none. All have an attitude toward this phenomenon. We can help most by making it clear that everybody does not have to become incapacitated with each cycle. A philosophy of acceptance of life is a great boon to many patients, who, otherwise, would be prepared to suffer upon the slightest provocation.

The problem of sterility concerns us here only because of the emotional reactions involved. While we investigate the cause for this disability it is extremely important that the process remain an investigation of both husband and wife. Deep feelings are involved in some people concerning their reproductivity and tremendous finesse is necessary to "save face" all around.

The indications for sterilization, as well as for termination of pregnancy, are best covered elsewhere, but we should remember that a few women do not want to accept further responsibility of more children, and would enlist our aid even in the absence of accepted medical criteria for these procedures.

Probably the most commonly overlooked illness in a busy practice is that psychosis which occurs about the involutional period of life. It is characterized not only by the symptoms of the menopause itself but by a sweeping depression as well. These depressive symptoms are those which most often go unnoticed, and too frequently result in suicide. These patients should be referred to a psychiatrist or a psychiatric hospital equipped to treat them. Such depressions are treatable and respond readily but are often overlooked because they appear at first to present only the usual findings of the menopause. This latter is a normal, physiological process through which every woman goes if she lives long enough. It is surrounded with much fabled tradition and is a cloak thrown over myriad ailments. We have all had patients referred as being in the menopause whose age, symptoms, and menstrual cycle made the diagnosis suspect. The poor old menopause gets credit and offers excuses for many unpleasant personality traits over which it has no control. The physical and endocrinological symptoms of the menopause are easily treated by the gynecologist. The depressive symptoms require special psychiatric treatment, to which they usually respond easily. If this differentiation is not made, the mortality can be high. Suicide is a dramatic and usually well-publicized result. A good rule of thumb for physicians to follow when patients tell of contemplating suicide is to believe they might. We see many patients who make suicidal threats, or gestures, apparently to spank someone. These gestures have been accidentally fatal in some cases. If a patient makes such threats, we would be well advised to consider them seriously and to protect ourselves at least to the extent of having the family share this responsible knowledge with us. We are all too familiar with the last line in the news item about the suicide's death: "She had been in ill health for some time." Awareness of the possibility can prevent the eventuality.

In summary, the gynecologist who can take time to listen to his patients, see them as more than dysfunctioning females, respect them as people, treat them honestly and with humility, will find his ability to help is greatly increased.

Index

A

Abdomen, examination of, 7
Abdominal pregnancy, 275
Abortion, 395
  habitual, 395
  incomplete, 396
  inevitable, 397,
  missed, 29, 396
  spontaneous, 395
  threatened, 396
  treatment, 396-7
  tubal, 268, 276
Abscess
  ovarian, 292
  pelvic, 255
  tubo-ovarian, 254, 291
Acne, 25, 28
ACTH, 38
Adenoacanthoma, 137, 188, 349
Adenocarcinoma
  cervix, 137
  endometrium, 178
  ovary, 316
  tube, 278
  vulva, 94
Adenofibroma, 299
Adenoma malignum, 179
Adenomyoma, 340
  uterus, 209, 340
  vagina, 92
Adenomyomectomy, 212
Adenomyosis, 209, 339
  rectovaginal septum, 347
  symptoms, 211
  treatment, 212
Adrenal gland, 30
  adrenal cortex, 31
  adrenal cortical hyperplasia, 31, 417
  adrenal cortical tumor, 32
  adrenalectomy, 31
  adrenalin, 30
  adrenal medulla, 30
Albright's disease, 161
Alcoholism, 456
Aldosterone, 38
Alexander suspension operation, 382
Amethopterin, 332
Aminopterin, 332
Amenorrhea, 27
  hypothalamic, 16, 169
  primary, 26, 168
  psychogenic, 169
  secondary, 17, 27, 169
Androgenic hormones, 34
Angle, posterior of bladder, 374
Anovulation, 162, 167, 438
Anteflexion of uterus, 375, 436
Antimetabolites, 332
Anuria, 390
Appendicitis, 260
Arborization, 22
Arrhenoblastoma, 33, 315
Arsphenamine, 42
Arterioles, spiral, 164
Arteriosclerosis, 29
Aschheim, 17
Aschheim-Zondek test, 37
Ascites, 264, 296, 325
Auto-inoculation, 40
Auto-transfusion, 278
Azoospermia, 440

B

Bacillus, crassus, 57
  Doederlein, 26
  Donovan, 47
  Ducrey, 47
Back, examination of, 14
Backache, 14, 379
Baldy-Webster suspension, 382
Bartholin glands
  abscess, 43
  acute infection, 44, 45
  chronic infection, 44, 45, 46, 47
  cyst, 45
  excision, 45
  fenestration, 44
  marsupialization, 44
Basal body temperature, 165, 441
Basal cell hyperplasia, 120
Basal metabolism, 33, 439
Biopsy
  breast, 7
  cervix, 111
  endometrium, 172
Bladder
  cystitis, 372
  ileal, 389
  incontinence, 372
  fistula, 388
  neurological, 372

Bleeding
  abortion, 394-399
  complaint, 171
  ectopic pregnancy, 276
  functional, 172
  hormones, 448
  intermenstrual, 172
  miscarriage, 408
  myoma, uterus, 141, 184
  polyp, 118
  postpartum, 423
  withdrawal, 30, 79
"Blue balls", 47
"Blutpunkte", 37
Boeck's sarcoid, 261
Bowen's disease, cervix, 120
  vulva, 71
Breasts
  aspiration, cyst, 7
  carcinoma, 29
  cysts, 29
  development, 28
  engorgement, 28
  papillary cystadenocarcinoma, 7
  papilloma, 7
Brenner tumor of ovary, 322
Bricker ileal pouch, 144
Broad ligament, varicose veins of, 215, 380
Bubo
  chancroid, 47
  climatic, 51
  tropical, 51

C

Calcification
  lithopedion, 267
  myoma, 203
  ovarian tumor, 299
Cancer (see carcinoma)
Candida albicans, 86
Carcinoma
  cervix, 137
    adenocarcinoma, 136, 137
    squamous cell, 137
  endometrium, 179, 183
  fallopian tubes, 278
  in-situ, 70, 123, 125, 126, 189
  ovary
    cystadenocarcinoma, 303
    granulosal cell tumor, 187, 318
    Krukenberg tumor, 310-312
    lymphosarcoma, 326
    papillary serous cystadenocarcinoma, 299, 305
    primary solid adenocarcinoma, 308-311
    pseudomucinous cystadenocarcinoma, 308, 309
    sarcoma, 326
      spindle cell, 326
      round cell, 326
  radiation therapy, 144, 195, 196
  Schiller test, 110
  spray, 140
  staging, 148
  urethra, 101
  vagina, 94
  vulva, 71
    adenocarcinoma, 71
    basal cell, 71
    metastatic, 73
    squamous cell, 71
Caruncle, urethral, 95
Castration, 31
Cauterization, cervix, 108, 111
  endometrial implants, 359
Cells, basophile, 17
  castration, 17
  chromophobe, 17
  clue, 89
  eosinophile, 17
  Langhan's, 394
  pro-granulosal, 318
  pro-thecal, 318
  thecal, 283
  reserve, 106
Cellulitis
  pelvic, 259, 260
  vulva, 71
Cervical os
  incompetent, 409
  occlusion, 116
  stricture, congenital, 116
    post-cauterization, 116
    post-conization, 116
Cervicitis, acute, 108
  chronic, 109
  cystic, 111
  eversive, 109
  gonorrheal, 108
  tuberculous, 263, 114
Cervix, 106
  adenocarcinoma of, 137
  amputation of, 115
    Schroeder, 116
    Sturmdorf, 114, 116
  anatomy, 106
  biopsy, 112
  Bowen's disease, 120
  carcinoma of, 134, 137
    adenocarcinoma, 137
    squamous cell, 135, 136
    symptoms, 141
    treatment, 143
  cervicitis, 108, 271
    acute, 108
    chronic, 109
    cystic, 111
    eversive, 109
    Schiller test, 110
  conization, Hyam, 111
    sharp, 111
  deciduoma of, 118
  development, 106

  dilatation, 116
  ectropion, 115
  endometriosis, 346
  epidermization, 119
  epidermoid carcinoma, 136
  erosion, 109
  eversion, 106
  gland invasion, 124
  laceration, 115
  leukoplakia, 127
  occlusion, 116
  palpation, 12
  polyp, 117
  pregnancy changes, 126, 127
  puberty, 107
  senile, 120
  squamous metaplasia, 119
  tuberculosis, 263, 114
Chancre, 40
Chancroid, 47, 48
Chemotherapy, 305, 331
Chief complaint, 4
Chlorambucil, 332
Cholesterol, 20
Choriocarcinoma, 406
Chorioma, 406
Chorioma destruens, 404
Chorionepithelioma, 72, 94, 406
Chorionic gonadotrophin, 18, 37, 394, 402
  Aschheim-Zondek test, 37
  Friedman and Lapham test, 37
  rat hyperemia test, 35
  frog test, 37
Chorionic villus, 394
Chromosomal sex, 412
Cigarette drains, 255
Climacterium, 447
Clitoris, 40
  carcinoma of, 72
  enlarged, 35, 316, 418
  hypertrophy of, 418
Coagulation necrosis, 406
Colposcope, 110
Colostomy, 393
  wet, 144
Colporrhaphy
  anterior, 365
  posterior, 364
Colpotomy
  posterior, 255
Compound E, F., 38
Condyloma accuminatum, 53
Condyloma latum, 42
Congenital abnormalities, 419
  cervix, 424
  tubes, 420
  uterus, 420, 427
  vagina, 420,425, 430
  vulva, 22, 23
Congestion, 23
  fibrosis syndrome, 215
  pelvic, 215
Conization
  Hyam's, 111
  sharp, "cold knife," 111, 129
Corpus luteum, cyst of, 285, 287
  life cycle, 288
  persistens, 288
  pregnancy, 271
Corpus uteri, carcinoma, 183
Corticosterone, 21
Cortisone, 32
Culdocentesis, 272
Culdoscope, 274
Culdoscopy, 274, 352
Cumulus oophorus, 283
Curettage
  Albright's, 30
  medical, 30, 173
  surgical, 172
  technique, 183
Cystadenoma
  papillary serous, 296, 298, 299
  pseudomucinous, 307
Cystadenofibroma, 299
Cystitis, 372
Cystocele, 364
  repair of, 243
Cysts
  chocolate, 343
  corpus luteum, 285, 287
  dermoid, 324
  endometrial, 293, 343
  functional, 295
  Gartner's duct, 30, 90, 296
  inclusion, 90
  lutein, 289
  microfollicular, 282, 285
  mucinous, 305
  Nabothian, 111
  Morgagni, 296
  multilocular, 296
  parovarian, 296
  psuedomucinous, 305
  sebaceous, 59
  serous, 295
  suburethral, 100
  theca-lutein, 291, 404
  tubo-ovarian inflammatory, 291
  vaginal, 90
Cytology, 145
  Papanicolaou smear, 8

D

Dark field examination, 41
Decidua, 8, 164
Decidual cast, 8, 272
Delerium tremens, 456

- Descensus uteri, 14
- Depression, 458
- Discharge
  - bloody, 171
  - cottage cheese, 86
  - mucous, 108
  - pubertal, 83
- Displacement, of uterus
  - acute anteflexion, 375
  - retrocession, 377
  - retroflexion, 377
  - retroversion, 352, 377
- Diuretics, 166
- Dmelcos
  - test, 47
  - vaccine, 47
- Doederlein bacillus, 26
- Donovan organism, 47, 50
- Douches, 263
- Ducrey bacillus, 47
- Dysgerminoma, 313
- Dysmenorrhea, 28, 34, 177, 211
- Dyspareunia, 63, 89, 351, 379, 452
- Dysplasia
  - cervical epithelium, 120, 122
  - fibrous, of bone, 161

E

- Ectopic pregnancy, 267-274
- Ectropion, 115
- Ejaculation, premature, 445
- Elephantiasis vulvae, 52
- Embolus, 259
- Emge suspension, 382
- Emotion, 16
- Endocervix, 137
- Endocervicitis, chronic, 113
- Endocrine therapy
  - dysmenorrhea, 178
  - growth uterus, 178
  - menopause, 448
  - menstruation, 166
  - sterility, 438
  - vaginitis, 80, 82, 85
- Endolymphatic stromal myosis, 223
- Endometrial biopsy, 172
- Endometrial hyperplasia, 22
- Endometrial cysts, 293, 343
- Endometrial polyps, 183, 451
- Endometriosis
  - bladder, 335
  - bowel, 346
  - bracheoradialis muscle, 348
  - cervix, 346
  - episiotomy scar, 347
  - experimental, 337
  - external, 342
  - fallopian tube, 346
  - implants, 342
  - inguinal canal, 346
  - internal, 210
  - laparotomy scars, 346
  - lymph nodes, 346
  - ovary, 292
  - pelvic, 346
  - peritoneal, 346
  - umbilicus, 346
  - uterosacral ligaments, 352, 438
  - vulva, 348
  - vagina, 91, 347
  - conservative operation for, 357
  - diagnosis, 343
  - lymphatic theory, 338
  - malignant change, 349
  - metastasis, 338
  - origin, 337
  - radical operation, 360
  - serosal theory, 337
  - stromatous, 223
  - treatment, 34, 356
- Endometritis
  - chronic, 399
  - syncytial, 399
  - tuberculous, 263
- Endometrium, 160
  - adenocarcinoma, 178
  - anovulatory, 161
  - atypical hyperplasia, 180, 189
  - carcinoma-in-situ, 179, 189
  - cyclic changes in, 161-164
  - decidua, 164
  - fallopian tubes, 346
  - histology, 164
  - interval phase, 163
  - menstrual function, 160
  - polyp, 183
  - postmenstrual, 163
  - premenstrual, 164
  - proliferative, 163
  - sarcoma, 222
  - spiral arterioles, 164
  - swiss-cheese, 172
- Enovid, 29
- Enterocele, 364
- Epidermization cervix, 119
- Epiphyscal closure, 28
- Episiotomy, 363
- Epithelium, 45
  - columnar, 106-110
  - germinal, 282
  - squamous, 106-110
  - transitional, 45
- Equine gonadotropin, 18
- Equilin, 26
- Erosion, cervical, 109
- Erythroplakia, 110
- Erysipelas, 60
- Erythroblastosis, 409
- Estradiol, 20, 25, 161
- Estriol, 25
- Esthiomene, 52

Estrogen, 20, 437
  assay, 35
  clinical uses, 25
  conjugated, 25
  cream, 82
  deficiency, 25
  intravenous, 168
  metabolic activity, 28
  pellet implantation, 25, 448
  production, 20
  therapy, 80, 82, 85, 166, 178
Estrone, 20, 25
Estrone sulfate, 26
Ethisterone, 26
Eventration, 144
Eversion of cervix, 106
Eviseration, pelvic, 144
Examination of patient
  abdomen, 7
  back, 14
  cervix, 8, 11
  general, 6
  genitalia, external, 10
    internal, 10
  ovaries, 12, 13
  pelvic, 3, 8, 9
  preparation and position, 6
  rectum, 14
  uterus, 12
  vagina, 14
  disposition of patient, 15
Extra-uterine pregnancy (see Ectopic pregnancy)

F

Fallopian tube, 13, 246
  anatomy, 246
  carcinoma of, 278
  development, 252
  endomestriosis, 270
  hysterosalpingogram, 437
  patency, 342
  Rubin's test, 437
  salpingitis, 247
  tuberculosis, 262
Fenestration, Bartholin gland cyst, 44
Fertility, 437, 438, 440
Fibroadenomatosis, breast, 25
Fibrocystic disease, breast, 25
Fibroma, ovary, 325-328
Fibromyoma
  uterus, 198
  vagina, 92
Fistula, 384
  intestinal, 268
  repair, 388
  rectovaginal, 390
  uretero-vaginal, 387
  urinary, 388
  vesico-vaginal, 387
Follicle stimulating hormone, 16, 17, 36
Follicles, primary, 283
  primordial, 283
Foreign body, vagina, 82
Fourchette, 40
Frei test, 51, 95
  antigen, 53
Freidman and Lapham test, 37
Frigidity, 34, 454
Fuadin, 48
Fulguration
  warts, 56
  endometrial implants, 357
Fungus infection, 86
Furuncle, 59

G

Gartner's duct, cysts of, 30, 90, 296
Gentian violet, 57
Genitalia, external, 8
  internal, 8, 9
Geriatrics, 28, 457
Gigantism, 17
Gilliam suspension, 383
Gland, adrenal, 30
  Bartholin, 8
  endocervical, 113
  endometrial, 163, 164
  pituitary, 17-20
  thyroid, 33, 34
Glycogen, 80
  cervix, 106
  endometrium, 163, 164
  vagina, 80
Goebel-Frankenheim-Steckel operation, 374
Gonadal agenesis, 23, 414
  dygenesis, 23, 168, 414
  failure, 36
Gonadotrophin, chorionic, 17, 37
  equine, 18
Gonorrhea, 42
Granuloma inguinale, 49, 51
Granulosal cell tumor, 161, 187, 318
Granulosa, zona, 30
Gumma, 42
Grave's disease, 33
Gyandroblastoma, 321
Gynechiatry, 453
Gynecography, 170

H

Hematocolpos, 424
Hematometrium, 116, 424
Hemorrhage (see bleeding)
Hermaphroditism, 411
Hermaphroditismus verus, 415
Herpes genitalis, 53
Hirsutism, 32
History taking, importance, 4
  suggested method for, 4
Hormone, 16
  adrenocorticotrophic, 38

  androgenic, 34
  assay, 35
  breast, 23
  chorionic, 394, 402
  estrogenic, 20
  equine gonadotrophic, 18
  follicle stimulating, 17
  genital growth, 22
  growth, 17
  lactogenic, 19
  luteinizing, 17, 19
  luteotrophic, 17, 19, 37
  menopausal, 19
  pituitary, 18
  progesterone, 23-25, 29, 30
  skin, 23
  steroid, 21
  therapy, for myomas, 208
  thyroid, 7, 33, 38
Hot flashes, 447
Huhner, postcoital sperm test of, 442
Hydatidiform mole, 399
  diagnosis, 402
  malignancy, 404
  ovarian changes, 404
  pathology, 401
  treatment, 402
Hydradenoma vulva, 75
17-Hydroxycorticoids, 38
Hydrosalpinx, 258
Hymen, imperforate, 431
Hyperemia test, 35
Hypernephroma, 94
Hyperplasia
  adenomatous, 182, 189
  adrenal, 425
  adrenal cortical, 31
  atypical endometrial, 182, 189
  basal cell, 120
  endometrial, 22
  reserve cell, 172
stromal, 283
  swiss-cheese, 172
Hyperthyroidism, 31, 33
Hypomenorrhea, 28, 167
Hypophysectomy, 31
Hypospadias, 417, 432
Hypothalamus, 16
Hypothyroidism, 33, 437
Hysterectomy, 208
  abdominal, total, 225, 226, 227
    technique, 232
  combined syndrome, 227
  indications for, 225-228
  radical, 144, 226, 227
  vaginal, 228, 371
    technique, 239, 240
Hysterogram, 342
Hysterosalpingography, 437, 442

I

Impotence, 455
Incontinence, stress, 372
  urgency, 372
Infertility, female, 435
  male, 440
Inflammatory disease, 257
Insemination, artificial, 445
  A.I.H., 445
  A.I.D., 445
Insufflation, perineal, 419
  tubal, 441
Intertigo, 59
Involutional melancholia, 457
Irradiation complications, 156
Irradiation sensitivity, 145
Irradiation therapy, 144, 304

K

Kelly stitch, 374
Keto-steroids, 38
Kleinfelter's syndrome, 414
Knee-chest position, 378
Kraurosis, 61, 66
Krukenberg tumor, 311-313
Kyphosis, 15

L

Labia majora, 40
Labia minora, 40
Laceration, third degree, perineal, 372
Lactation, suppression of, 28
Lactobacillus, 80
Langhan's cells, 17, 394
Leiofibromyoma, 198
Leiomyoma, 198
Leiomyosarcoma, 198
Leukoplakia, cervix, 127
  vulva, 63-66
Leucorrhea, 108
L.H., 17, 36, 289
Lichenfication, 61
Lichen sclerosis et atrophicus, 66
  children, 67, 69
  vulva, 69
  pathology, 66
Ligaments
  broad, 215
  cardinal, 366
  round, 344, 346
  uterosacral, 348, 366
  varicose veins, 380
Lipschütz, acute ulcer of, 57
Liquor folliculi, 285
Lordosis, 15
L.T.H., 17, 37, 289
Lugol's solution, 110
Luteoma, 321
Luteotrophin, 17, 19, 37
Lymphogranuloma venereum, 51-53
Lymphopathia venereum, 51

M

Macrogenitosomia praecox, 161, 418
Manchester-Fothergill operation, 371
Marshall-Marchetti operation, 374
Masculinovoblastoma, 322
Mastitis, chronic cystic, 25, 166
Masturbation, 456
Melanoma, vulva, 76
Menarche, 161
Menometrorrhagia, 27, 34, 205, 208
Menopause, 447
  symptoms, 447
  treatment, 448
Menorrhagia, 20, 175, 177, 205, 211, 291
Menstruation, 160
  anovulatory, 27, 162, 167, 438
  hormones, 24
  induced, 30, 174
  precocious, 161
  retrograde, 337
  theories, 160
  vicarious, 166
Mering operation, 61
Mesenchymomas, feminizing, 321
Mesonephroma, 324
Metaplasia, squamous, 106
Metastases, 138, 181, 194, 287, 310
Methylbis, 331
Metrorrhagia, 29, 171, 176, 205
Millen operation, 374
Miscarriage, 408
Mineralization, anabolic, 28
Mittelschmerz, 164, 286
Mole, hydatidiform, 399
Monilia, 86
Mons veneris, 40
Morgagni, cysts of, 296
Mucometrium, 116
Mucus, cervical, 22
Mucous patch, 42
Mullerian duct, 419
Myomas, 198, 437
  cellular, 220
  diagnosis of, 206
  hormone therapy for, 208
  sarcoma, 203, 217
  submucous, 200
  symptoms of, 205
  treatment of, 207
Myomectomy, 208
Myometrium, 22
Myosis
  endolymphatic, 223
  stromal, 223
Myxedema, 33

N

Neisseria sicca, 81
  gonorrhea, 81
Neurectomy, presacral, 359
Nitrogen mustard, 331
Noma, 60
Norethindrone, 29
Norethynodril, 29
Norlutin, 29
Nystatin, 57

O

Obesity, 456
Oligomenorrhea, 28, 167
Olshausen suspension, 382
Oophoritis, 291
Ophthalmia, 81
Osteoporosis, 28, 34
Ova, primordial, 283, 343
Ovarian agenesis, 168
  dysgenesis, 168
Ovary, 20, 282
  abscess, 292
  adherent, 293
  adrenal rest, 322
  arrhenoblastoma, 315
  Brenner, 322
  cystadenofibroma, 299
  dysgerminoma, 313
  endometriosis of, 292, 293
  feminizing mesenchymomas, 321
  fibroma, 325
  granulosal cell tumors, 187, 318
  gyandroblastoma, 321
  hilus cell tumor, 322
  histology of, 282
  luteoma, 321
  lymphosarcoma, 326
  masculinovoblastoma, 322
  mesonephroma, 324
  metastatic carcinoma of, 310
  papillary cystadenoma, 293
  papillary serous cystadenocarcinoma, 296, 299
  papilloma, 296
  psuedomucinous cyst, 307
  sarcoma, 326
  seminoma, 313
  Stein-Leventhal, 282
  stromal hyperplasia, 283
  teratoma, 325
  testicular adenoma, 316
  thecoma, 321
  tumors of, 294, 313
  "warty," 298
  wedge resection of, 170, 282
Ovulation, 164
  inhibition, 28
  pain, 286
Oxysteroids, 38

P

Paget's disease, vulva, 71
Papanicolaou
  cytology, 7, 8, 280
  techniques, 7, 8

Paracentesis, 296
Paroophoron, 296
Parovarian cyst, 296
Pedicle, torsion, 327
Pediculosis pubis, 60
Pelvic, abscess, 255
  cellulitis, 259
  congestion, 215
  hematoma, 271
  inflammatory disease, 247
  pain, 206, 209
Penicillin, 42, 81, 252
Perirenal insufflation, 33, 419
Peritonitis
  appendicitis, 255
  gonorrheal, 252
  tuberculous, 264
Pessary
  Gelhorn, 365
  Hodge, 365
  Smith, 365
  stem, 117
Phase, menstrual cycle
  early interval, 163
  late interval, 164
  post-menstrual, 163
  premenstrual, 164
  proliferative, 163
Phenyl mercuric acetate, 57
Phlebitis, 257
Pineal tumor, 161
Pinworm, 81
Pituitary gland
  anterior lobe, 17
  cells, 18
  hormones, 19
  failure, 36
  posterior lobe, 17
Placenta, 394
Podophylin, 56, 95
Polyp
  cervical, 117
  endometrial, 183, 451
  placental, 398
Position
  knee-chest, 380
  Sims left lateral, 388
Pregnancy, 394
  abdominal, 267, 268
  abortion, 395
  carcinoma-in-situ, 126
  chorionepithelioma, 404
  cornual, 267, 268
  ectopic, 267, 268
  hydatidiform mole, 401, 402, 403, 404
  interstitial, 268
  isthmal, 268
  myomas, 205
    operation, 205
  ovarian, 268
  tests, 37
  tubal, 269, 270
Pregnandiol, 36
Pregnantriol, 38
Premarin, 90, 444
Premarital counselling, 457
Premenstrual tension, 25, 165
Prepuce, 40
Procidentia, 366
Progresterone, 26, 30
  amenorrhea, 29
  assay for, 36
  clinical use, 29
  induced menstruation, 174
  medical curettage, 173
  metrorrhagia, 29
  norethynodrel, 29
  norethindrone, 29
  secretory effects of, 173, 174
Prolan A, 17
  B, 17
Prolapse, 14
  degree, 228, 366
Propionic acid, 57
Protein-bound iodine, 38
Pruritus vulvae, 61
Pseudohermaphroditism, 411
Pseudomucinous cyst, 305
Pseudomucinous cystadenoma, 307
Pseudomucinous cystadenocarcinoma, 307
Pseudomyxoma peritonei, 306
Psychosis, 456, 457
  postpartum, 456
Psychotherapy, 439, 454
Puberty, precocious, 319
Pyocolpos, 424
Pyometrium, 116, 424
Pyosalpinx, 263

R

Radiation curability, 144
"Radiation response" (RR), 144
Radio-active gold, 305
Radio-insensitivity, 71
Radium
  preoperative, 195
  therapy, 195
"Randbelag," 123
Rectocele, 363
Rectovaginal septum, 391
Rectum, 14
Reinecke crystals, 322
"Reserve cells," 106
Rete ovari, 315
Retention, water, 25, 165
Retrocession, uterus, 377
Retroflexion, uterus, 377
Retroversion, uterus, 352, 377
Rubin's test, 437, 441

S
Salpingitis, 437, 248, 252
  acute, 249, 252, 256
  chronic, 256
  diagnosis, 248
  gonorrheal, 247, 252, 342
  isthmica nodosa, 258
  post-abortal, 257
  post-appendicitis, 259
  post-delivery, 257
  subacute, 248, 253
  tuberculous, 260-266, 443
Salpingostomy, 443
Sarcoma
  botryoides, 94, 222
  endometrium, 178
  myoma, 198
  uterus, 217
Scabies, 60
Schiller test, 110
Scoliosis, 15
Sedimentation rate, 254
Semen analysis, 440
Seminoma, 313
Sensitivity response (SR), 144
Septicemia, 257
Serologic tests, 41
Sex
  body, 413
  chromosomal, 412
  genital, 413, 416
  germinal, 413
  gonadal, 413
  instructions, 457
  psychologic, 416
  rearing, 416
Sexual compatability, 455
  development, precocious, 161
  deviation, 456
  drive, 456
Shedding
  irregular, 176
Shock, 270
Sims-Huehner test, 436, 442
Sim's position, 388
Skene's ducts, 42, 47
Smegma, 139
Sodium depletion, 417
Spaulding-Richardson operation, 371
Speculum
  Graves, 8
  Sims, 388
Spermatazoa, 436, 440
Sphincter
  relaxed vesical, 373
Spina bifida, 368
"Spray carcinoma," 140
SR, 144
Stein-Leventhal syndrome, 169, 282, 284
Sterility, 435
  anovulatory menstruation, 438
  artificial insemination, 445
  basal body temperature, 165, 441
  basal metabolism, 439
  cervicitis, 436
  congenital anomalies, 436
  displacement uterus, 437, 438
  endometriosis, 438
  hysterosalpingography, 437, 442
  male factors, 440
  myoma, 206, 437
  psychogenic factor, 439
  Rubin's test, 437, 441
  semen analysis, 440
  surgery, 443
  thyroid extract, 439
  treatment, 440
Stilbestrol, 26, 174
Strassman operation, 427, 436
Streptobacillus, Ducrey, 47
Streptococcus subacidus, 88
"Stress diseases," 30
Strictures
  cervical, 116
  rectal, 52
Stromal myosis, 223
Struma ovarii, 325
Stromatous endometriosis, 223
Suicide, 458
Sulfonamides, 81
Suspension uterus, 382, 384
Syncytium, 394
Syncytioma, 399
Syndrome
  combined, 227
  congestion fibrosis, 217
  Kleinfelter's, 414
  Meig's, 325
  Stein-Leventhal, 169, 282, 284
  Turner, 416
Syphilis, 40
  chancre, 40
  condyloma latum, 42
  dark-field examination, 41
  histologic appearance, 42
  mucous patch, 42
  primary, 40
  secondary, 42
  serologic tests, 42
  tertiary, 42
  treatment, 42

T
Tartar, emetic, 48
TEM, 331
Temperature
  basal, 441
  variation, 16
TEPA, 305, 331
Teratoma, 305, 325

Test
  pregnancy, 37
  Rubin's, 437, 441
  Sims-Huehner, 436, 442
  VDRL serologic, 42
Testicles, undescended, 18
Testosterone, 21
  methyl, 34
  propionate, 34, 177
  rebound phenomenon, 444
  therapy, 34
Theca
  externa, 284
  interna, 283
Thecoma, 321
Theelin, 25
THIO-TEPA, 305, 331
Thrombosis, coronary, 29
Thrombophlebitis, 267
Thyroid, 7, 33
  extract, 174, 397, 439
  function, 33
  hormone, 38
Tinea cruris, 60
Tranquillizers, 456
Transuterine tubal insufflation, 437
Treponema pallida, 41
Trichomonas vaginalis vaginitis, 83, 85, 95, 108
Triethylene melamine, 332
Triethylene phosphoramide, 305, 331, 332
Triethylene thiophosphoramide, 305, 331, 332
Trigonitis, 104
Tri-iodothyronine, 38
Trophoblast, 394
TSPA, 305, 331
Tubal obstruction, 441
Tuberculosis
  cervix, 263
  endometrium, 263
  miliary, 267
  peritonitis, 264
  salpingitis, 260, 261, 263, 443
Tumors
  adrenal, 322
  Brenner, 322
  cervix, 117
  dysontogenetic, 313
  endometrium, 184
  granulosal cell, 161, 187, 318
  hilus cell, 322
  Krukenberg, 311
  mixed mesodermal, 222
  myometrium, 198-202
  ovary, 294-326
  pineal, 161
  tube, 278
  vagina, 90-94
  vulva, 71-73
Turner's syndrome, 416

U

Ulcus actum vulva, 57
Ureterostomy, 390
Urethra, 8
  carcinoma, 101
  caruncle, 95
  diverticulum, 97
  female, 94-104
  fistula, 388
  incontinence, 372
  inflammation, 95, 96
  polyp, 104
  prolapse, 97
  trichomonas vaginitis, 95
  tumors, 101
  venereal diseases, 94
  venereal lymphogranuloma, 95
  verruca acuminata, 95
Urethritis, chronic, 104
Urine
  incontinence of, 371
  residual, 365
  stress incontinence, 372
  urgency incontinence, 372
Urogenital sinus, 416, 419
Urothane, 333
Uterus
  acute anteflexion of, 177, 375-377, 436
  adenoacanthoma, 349
  adenomyosis of, 209-211, 437
  anomalies, 428, 429
  carcinoma, 183
  descensus, 14, 374
  didelphys, 422
  dilatation and curettage of, 183
  displacements, 377-381
  fibrosis of, 214
  hypoplasia, 28, 436
  increased growth of, 445
  infantile, 436
  lipoma, 203
  mixed mesodermal tumors of, 222, 223
  myomas of, 198, 437
    calcifying degeneration of, 201
    carneous degeneration, 201
    fatty degeneration, 201
    fibroid, 198
    fibromyoma, 198
    hyaline degeneration, 201
    leiofibromyoma, 198
    leiomyoma, 198
    malignant degeneration, 201
  placental polyp, 398
  procidentia, 366
  prolapse of, 366
  retrocession, 377-381
  retrodisplacements, 377-381, 437
  retroversion, 352, 377
  sarcoma, 217-221

  size of, 209
  subinvolution, 212
  submucous myoma, 200
  suspension of, 381
  ventral fixation, 381

V

Vaccine
  Dmelcos, 47
Vagina
  absence, 420, 433
  adenocarcinoma, 94
  adenomyoma, 92
  artificial, 420
  atrophic, 89
  carcinoma, squamous cell, 92
  chorionepithelioma, 94
  construction of, 420
  cultures, 80
  cysts, 90
  double, 420, 431
  endometriosis, 91
  estrogenic, 83
  fibromyoma, 92
  foreign bodies, 82
  Gartner's duct cyst, 90
  hypernephroma, 94
  inclusion, 90
  malignant tumors of, 92, 93
  metastatic carcinoma, 94
  postmenopausal atrophy, 89
  sarcoma, 94
  septate, 425
  secondary carcinoma, 94
  vaginitis, 86, 88, 452
  washing, 10, 80
Vaginal outlet
  lacerations, 115
  relaxed, 363
Vaginal wall, 94
Vaginitis
  atrophic, 452
  fungus, 83, 86
  gonococcal, 80
  haemophilus vaginalis, 88
  monilia, 86
  non-specific, 88
  postmenopausal, 89
  prepubertal, 79
  trichomonas vaginalis vaginitis, 83, 85, 89, 93
Varicose veins, broad ligaments, 215, 380
VDRL serologic test, 42
"Velvety mass," 14
Venereal disease, 94
Venereal wart, 53
Venereum lymphogranulum, 51
  lymphopathia, 51
Ventral fixation, 381
Verruca accuminata, 95
Vesico-rectal band, 421
Vestibule, 40
Vincent's disease, 53
Vincent's organisms, 53
Virginity, 453
Virilism, 417
Virilizing effect, 31
Vitamin A, 66
Vulva, 40
  adenocarcinoma of, 73, 94
  Bowen's disease, 71
  carcinoma of, 65, 71
    basal cell, 71
    carcinoma-in-situ, 69
    excision, 71
    metastatic, 73
    microscopic, 71
    squamous cell, 71
  cellulitis, 60
  chancre, 40
  chancroid, 47
  chorionepithelioma, 72
  condyloma accuminatum, 53
  condyloma latum, 42
  elephantiasis, 52
  endometriosis, 348
  fibroma, 73
  granuloma inguinale, 47, 49
  hydradenoma of, 75
  kraurosis, 61, 62
  leukoplakia, 63-66
  lymphogranuloma venereum, 51, 52, 53
  melanoma, 76
  neurogenic disease of, 61
  Paget's disease, 71
  pruritus, 61
  sarcoma of, 75
  sebaceous cyst of, 59
  syphilis, 40
  tuberculosis of, 60, 263
  ulcus acutum, 57
  venereal disease, 40
Vulvectomy, radical, 71
  simple, 66
Vulvitis, 57
  diabetic, 61
  diphtheritic, 58
  follicular, 58, 88
  gangrenous, 60
  monilial, 57
  trichomonal, 58

W

Walking temperature, 165, 441
Water retention, 165
Web neck, 416
"Witches milk," 79
Withdrawal bleeding, 30
Wolffian ducts, 414

Z

Zona basalis, 164
Zona compacta, 164
Zona reticularis, 31
Zona spongiosa, 164
Zondek, 37
Zone, reticular, 418